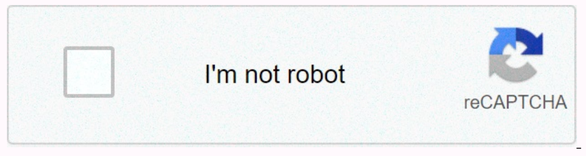

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New antimalarial drugs pdf

p. 252. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. It also reviews the development and spread of drug resistance, the methods used to assess the presence and level of drug resistance, and the extent to which chloroquine and sulfaxine/pyrimethamine (SP), the two most widely used antimalarial medicines in the modern world, have now lost effectiveness. Malaria sickens and kills people using several pathological mechanisms, understood to varying degrees. In addition to the treatment of first- and second-line antimalarial medicines, additional and supportive care measures may be required (e.g. intravenous fluid, blood transfusion, supplemental oxygen, anti-resuspension). The aim of treatment is to prevent death or long-term deficiency from malaria, reduce the incidence of an episode of acute disease and completely clear the infection so that it does not resevere. Fever, sweating, and chills (or, in some cases, just fever) caused by the release of plasmodia into the bloodstream from mature blood schizonts, are the most common symptoms of heralding the onset of a clinical case of uncomplicated falciparum malaria (see chapter 6 on a description of the development of clinical symptoms). Without treatment or active immune Page 253 Share Cite Recommended quote: 9 Antimalarial Drugs and Drug Resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. Mature infection may include up to 1,012 circulating plasmodia. Any time after the infection is formed, most plasmodia will at some stage of abreathless maturation result in another round of multiplication of the patient's bloodstream. However, some parasites will be transformed into sexual stages (gametocytes), which, when swallowed by mosquitoes, can perpetuate the transmission cycle. Because each stage of the life cycle of malaria has different biochemical and different properties (i.e. it expresses different proteins or finds different parts of the body), the drug can kill one stage, but it has little effect on another. In other words, at each stage of the life cycle, the parasite manifests itself in unique biological properties that can offer a target for action on one or more antimalarial drugs. Currently available antimalarials are to be divided into three broad categories according to their chemical structure and mode of action (Add- 9-A): aryluminoalcholic compounds: quinidine, chloroquine, amodiaquin, meflixin, halofantrine, lymephanthrin, piperacine, taphenoquin Antifolo compounds (antifols): pyrimethamin, proguanil, chlorproguanil, trimethoprim artemisinin compounds (artemisinin, dihydroartemiin, artemetheter, aseest) Atovaquone are a group of anti-malmalmalasus with a unique mode of action; together with the proguatil it is sold under the trade name Malarone®. Several antibacterial drugs (eg, tetracycline, clindamycin) also have antiplamic activity, although in general their action is slow in the treatment of malaria (as opposed to prevention); it is only recommended in combination with other antimalarial medicines. Drugs that act against Plasmodium falciparum also work against the other three malaria species that affect humans-P. vivax, P. malaria, and P. ovale-except antifols, which works poorly against P. vivax. Current treatment protocols for uncomplicated malaria and severe malaria are given in tables 9-1 and 9-2. p. 254. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. Followed by: 5 mg/kg at 12, 24 and 36 h; or 10 mg/kg at 24 h, 5 mg/kg 48 h or Amodiaquine 10 mg base/kg/day for 3 days1 chlorquine resistant P. falcipare known to be susceptible to sulfadoxinisetrimethamine (SP) Pyrimethamine 1,25 mg/kg + sulfadoxine 25 mg/kg (single dose; 3 tablets for adults) or Amodiaquine 10 mg base/kg/day for 3 days for chloroquine tracker P. vivaxb and multi-resistant P. falciparum Oral 4 mg/kg/day for 3 days + meflovin 25 mg base/kg (15 mg/kg on Day 2, 10 mg/kg on day 3) Arteter-lumefantrine 1.5/9 mg /kg twice daily for 3 days with food Quinine 10 mg salt/kg three times daily plus tetracycline 4 mg/kg four times daily or doxycycline 3 mg/kg once daily or clindamycin 10 mg/kg twice daily for 7 days2masking the combination of falciparmalarial combinations containing an artemisin derivative. Artesin (4 mg/kg/day for 3 days) has been successfully combined with chloroquine, amodiaquin, SP, meffoquine and atovaquone proguane. bIt applies to genuinely resistant P. vivax infections, which are a major problem only in Oceania and Indonesia, and should not be confused with relapses. Amodiaquine is more effective than chloroquine resistant P. vivax. Drug interactions with people who take them, as compounds are absorbed, metabolized, distributed and excreted, called pharmacokinetics. Antimalarial drugs vary greatly in their pharmacokinetics, which affects how well they work, how they are dosed, and how long they should be taken. People also how they respond to drugs. Some of these reactions are genetically determined, others by health, others by dietary factors. In general, the pharmacokinetic properties of antimalarials are similar in children and adults, although metabo-Page 255 Share Cite Recommended quote: 9 Antimalarial drugs and drug resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × General points A. There are now some places in the world where chloroquine can be relied on for falciparum malaria, and SP resistance is spreading rapidly, so if this drug is used, up-to-date information on drug susceptibility is required. Amodiaquin is more effective than chloroquine against chlorquinorestent P. falciparum, while highly amodiaquine-resistant parasites are common in East Asia. B. Pregnancy: There are insufficient data on the safety of most antimalarials during pregnancy. Artemisinin and its derivatives must not be in the first trimester. Halofantrine, primaquine and tetracycline should not be used during pregnancy. There are theoretical concerns about triggering kernicterus when long-acting sulphonamides are being used in the near future, but there is no evidence that this is a major problem in practice. There are uncertainties about the safety of meflomin during pregnancy. Quinine, chloroquine, proguane, SP and clindamycin are considered safe during the first trimester. Quinine may cause hypoglycaemia, especially during late pregnancy. C. Vomiting is less likely if the patient's temperature is lower before oral administration. D. If possible, artesulate or quinine should be combined with tetracycline or clindamycin. Short courses of artesunate or quinine (< 7 days) alone is not recommended. E. In case of renal insufficiency. after 48 hours, the quinine dose should be reduced by one and a half thirds and doxycycline should be prescribed, but not tetracycline. F. All drug doses in children do not change: however, several drugs, including atovaquone, proguanil and artesulate, have significantly altered kinetics during pregnancy. Special points 1. Patients with P. vivax and P. ovale infections should also take primary priquine 0.25 mg base/kg/day (base 0.375-0.5 mg/kg in Oceania) for 14 days for 14 days to prevent relapse. In mild G6PD deficiency, 0.75 mg base/kg should be administered once weekly for 6 weeks. In the case of severe G6PD deficiency, primahine should not be used. 2. None of the tetracyclines should be used in pregnant women or children under 8 years of age. multiple drug lyms during pregnancy (e.g. atovaquone, mefloquine, cyloguanil). The main pharmacokinetic properties of antimalarials is how long they remain in the body. Artemisinin and its derivatives are absorbed and excreted most imply (half-life = 1 hour or less). Quinine is also absorbed and eliminated during one parasitic life cycle (11 hours in healthy subjects up to patients with severe malaria). Other antimalarials are eliminated very slowly, remaining at significant concentrations for several days (pyrimethamine, halofantrine, luophantrtin, atovaquone) or even weeks (mefloquine, chloroquine and piperakin). In general, fast-excreted drugs (artemisinin, and quinine) should be transferred to four aborn cycles (7 days) to provide a cure for non-immune patients. In contrast, the drug that has Page 256 Share Cite Suggested Quote: 9 Antimalarial Drugs and Drug Resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × 9. Treatment of severe malaria health clinic: Hospital intensive care unit (Icu) No intravenous infusion possible rural health clinic: No injection option for chloroquinos resistant P. falciparum quinine dihydrochloride 7 mg of salt/kg in 30 minutes, followed by 10 mg/kg immediately within 4 hours; 20 mg of salt/kg administered within 4 hours. Maintenance dose: 10 mg salt/kg administered over 2 to 8 hours at an 8 hour interval quinine dihydrochloride 20 mg salt/kg diluted 1:2 with sterile water administered by split injection on both front of the abdomen. Maintenance dose: 10 mg/kg for 8 hours 10 mg quinine base/kg administered as an infusion over 1-2 hours followed by 1.2 mg base/kg/hourb Electrocardiographic monitoring Recommended Page 257 Part Cite Recommended hardening:9 Antimalarial drugs and drug resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × Artemisinin derivatives Artemether 3,2 mg/kg stat.m. 1.6 mg/kg/day: Artesunate 2.4 mg/kg stat.m. then a day known chloroquinol-sensitive P. falciparum chlorquina 10 mg base/kg administered intravenously at a constant rate of 8 hours followed by 15 mg base/kg over 24 hours chloroquine 3,5 mg base/kg for 6 hours or 2,5 mg base/kg over 4 hours at i.m or s.c A total dose of 25 mg base/kg 10 mg/kg/day or nasogest chloroquine as oral use The desired dose interval for parenteral quinine in African children is 12 hours. bSome authorities recommend a lower dose of 6.2 mg base/kg at baseline within 1 hour followed by 0.012 mg base/kg/hour. There are insufficient data on confident dose recommendations. General points A. If in doubt, the infection is considered to be chlorhinos-resistant. There are very few places where chloroquine can now be relied on. B. Infusions can be given in 0.9% saline solution, 5% or 10% dextrose/water. C. The rate of infusion of quinoline antimlars should be closely monitored. D. Oral treatment should be initiated as soon as the patient can swallow with sufficient confidence to complete end of the course of treatment. p. 258. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. Halofantrine, lumephanthrin, atovaquone and, to a much lesser extent, mefloquine, are hydrophobia and lipophilised (i.e. insoluble in water and able to dissolve fat); as a result, their absorption also varies depending on the amount of dietary fat consumed. For this reason, the blood concentration of this medicine may vary considerably depending on whether the same dose is followed. The way drugs act on its purpose, in this case, plasmodia-called pharmacodynamics. The main effect of antimalarial drugs for uncomplicated malaria is to inhibit parasite reproduction by killing parasites. If the untreated infection progressed to maximum efficacy, with each life cycle, the total body parasite load would increase by a multiplication rate that would bring the average number of viable parasites closer to the average number of mature schizont (18-36) (White, 1997). The proliferation of parasites in non-immune individuals often occurs at a multiplication rate of 6 to 20 per 2 day cycle (30-80 percent efficacy). Antimalarial drugs with maximum effect (Emax), on the other hand, reduce the total number of parasites 10 - to 10,000 times per cycle. Individual antimalarial drugs differ in their Emax (i.e. part of the total plasmodia killed in one treatment); for example, artemisinins often yield 10,000 times the cut for each aborn cycle, while antimalarial antibiotics such as tetracycline or clindamycin can only reach 10 times the parasite reduction cycle. The lowest blood or plasma concentration of antimalarial drugs that cause Emax can be considered as a minimum parasitic concentration (MPC). The reduction of parasites appears to be a first-order process throughout (Day et al., 1996), which means that a fixed part of the infectious malaria parasite population is removed in each subsequent cycle, provided that the MPC is exceeded. Patients with acute malaria may have up to 1,012 parasites circulating in the blood. Even with a kill rate of 99.99 percent per cycle, at least three life cycles (6 days) are required to completely eradicate parasite loads; therefore, the concentration of therapeutic drugs should be 4 cycles to carry out the cure (White, 1997, 1998). Simply put, patients taking rapidly removed medicines should continue treatment throughout the week. Treatment responses are always better in patients with some immunity (York and Macfie, 1924), because immune responses kill parasites much the same as Page 259 Share Cite Recommended Quote: 9 Antimalarial Drugs and Drug Resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of the Malaria Drug Age Washington, DC: National Academy press. doi: 10.17226/11017 × do. In endemic areas, the worst treatment outcomes can be seen in young children with low immunity. By contrast, although their degree of immune protection cannot be determined or accepted, older children or adults in high-transmission areas can do surprisingly well with failed drugs because much of their therapeutic response stems from immunity rather than antimalarial drug activity. In severe falciparum malaria, the stage in which the action of antimalarial drugs is especially important, because the ultimate goal of treatment is to stop parasites maturation at a late stage, cytoherent parasites (i.e. mature schizonts that attach endothelium cell lining to small blood vessels), which are primarily responsible for life-threatening complications. Artemisinin derivatives are beneficial because they prevent parasites from maturing to these more pathological stages, while quinine and quinidine do not affect parasites until they are already quoted. Antifols work even later in the cycle and are not recommended for severe malaria (Yayon et al., 1983; ter Kuile et al., 1993). None of the drugs will prevent rupture and reinsulination of infected red blood cells when schizont is formed. New types of ring-shaped (i.e. early aborn parasites) are also relatively drug resistant, especially in quinine and pyrimemamine. Artemesin derivatives offer the most extensive antimalarial action against the stages of development and the fastest in vivo activity (ter Kuile et al., 1993; Baltais, 1997). These compounds (and to a lesser extent chloroquine) prevent the depration, incurs clearance of ring stages and prevent the abnormality of terminal organs that would otherwise occur if cytopenia progresses uncontrolled (Chotivanich et al., 2000). Pyrimethamine and biguanides, such as chlorocyanic, affect folic acid synthesis by inhibiting a parasite enzyme called dihydrofolate reductase reductase-thymyidine synthase (DHFR). Sulphonamides act in the previous stage by folic acid by inhibiting the parasite enzyme dihydropteroate synthase (DHPS). There is a strong synergy between these two classes of drugs when they are together. However, resistance to pyrimemamine P. falciparum developed within a few years after its introduction (Peters, 1987) due to the point mutation of the DHFR gene, which causes 100- to 1,000 times reduced affinity of the enzyme complex on the drug. Progressive mutations of the P. falciparum dhfr gene further reduced efficacy. Triple mutant infections are relatively resistant to antiphatate therapy; with a fourth mutation in the malaria parasite, antiphate drugs become completely ineffective. p. 260. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/1101 ×7 P. falciparum strains are now common in parts of Southeast Asia, and South America (Imwong et al., 2001). Resistance to partner antifols sulphonamide and sulfon is acquired by gradually obtaining mutations in the P. falciparum gene coding target enzyme DHPS. One of chloroquinoc's most dramatic properties is its ability to concentrate from nanomolar (10-9) levels outside the parasite to levels one million times higher (millimolarity, 10-3) acidic food vacuole from the parasite inside red blood cells (Krogstad and Schlesinger, 1987). However, this action does not in itself explain the antimalarial activity of chloroquine. Chloroquine works by interfering with heme dimerization, a detoxifying biochemical process of malaria parasite, which usually yields malaria pigment (hemozoin). Reduced intracellular drug concentrations accompany chlorquin resistance as resistant parasites expel chloroquine from acid feed vacuols 40-50 times faster than drug-sensitive parasites (Bray et al., 1998). Such accumulation deficit was once associated with a change in the pH gradient or a change in membrane permeability, or both (Le Bras and Durand, 2003). However, chlorhinoquine resistance was found to be reversible with verapamil, a drug that also modulates multi-resistant (MDR) mammalian cancer cells. This discovery led to the identification of the protein Pgh1 (an analogue of exaggerated glycoprotins that expel cytotoxic drugs in cancer cells) in the digestive vacuole membrane P. falciparum. P. falciparum (pfmdr1) are specified genes that encode MDR proteins; the enhancement of these wild-type MDR genes has recently shown to be caused by mefliline resistance (Price et al., 1999b). The point mutation in the gene that encodes the food vacuole transporter protein (pfcrt) is associated with chloroquine resistance (Durand et al., 2001; Warhurst, 2001) and corulate with reduced in vivo chloroquine efficacy (Djimde et al., 2001). In the presence of Pfcrt mutations, the second transporter (Pfmdr1) of the mutation further modulates in vitro resistance, although the role of Pfmdr1 mutations in determining in vivo responses to chloroquinosis therapy remains unclear. Additional unbound mutations may be involved in the development of chloroquine resistance, some of which have not yet been identified. In the laboratory, the exhaust mechanism seen in chloroquine-resistant P. falciparum parasites may inhibit several unbound drugs (calcium channel blockers such as verapamil, as well as tricyclic antidepressants, phenothiazines, and antihistamines), while mefloquine resistance may be Page 261 Share Cite Recommended Citation: 9 Antimalarial drug and drug resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. Oduola et al., Oduola et al., Clinical applications from these findings are few to date, although chloroquine plus high doses of chlorpheniramine (antihistamine) had shown better efficacy against chloroquinorezistentu P. falciparum in Nigerian children (Sowunmi et al., 1997). Whether the general use of resistance reversal will be safe and possible in the future remains an open question (Personal Communication, N. White, Mahidol University, March 2004). In general, antimalarial drug resistance to mefliline, quinine, lymefanthrin and halofantrine is associated, but chloroquine and resistance to meflixin are not. Resistance between antimalarials is linked to the common aspects of their activities, as well as to the mechanisms of resistance. Parasites with high levels of chloroquine resistance (in southeast Asia) are generally also resistant to amodiaquin; The population of Southeast Asia amodiaquin may thus fail as aid treatment (Le Bras and Durand, 2003). The same relationship applies to halofantrine and meflixin. On the other hand, there may be an inverse correlation between chloroquine and mefliquin sensitivity: in Africa, for example, chloroquin-sensitive strains are significantly less susceptible to mefliline or halofantrine, and vice versa (Oduola et al., 1987; Simon et al., 1988). Atovaquone is malarone® ingredient, a new combination of drugs (consisting of atovaquone and proguanil) used to treat and remove chloroquine-resistant P. falciparum. Atovaquone interferes with the transport of mitochondrial electrons and blocks cell breathing (Srivastava et al., 1997). High levels of atovaquone resistance arise from one point mutations in the gene encoding cytochrome b found on a small, extrachromatomal DNA-containing element in a parasite (Korsinczky et al., 2000). From available antimalarial means, artemisinins are effective in killing the widest range of aborn-stage parasites, ranging from medium-sized rings to early schizonts; they also produce the fastest therapeutic response by accelerating the clearance of circulating ring-stage parasites (ter Kuile et al., 1993). Qinghaosu or artemisinin is a sesquiterpene lactone peroxide that is extracted from the leaves of the shrub Artemisia annua (qinghao). Three derivatives are widely used: oil soluble methyl ether, artemether (artemotil [arteether] is a closely related compound); water-soluble hemi-used derivative, artesulate; dihydroarteminin (DHA). p. 262. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × Artesunate, artemether, and arteether are all synthesized from DHA, and they are converted back to their body. Artemisinin itself is available in some countries in Asia. It is 5-10 times less active than derivatives and is not metabolised to Artemisinin is available as powder capsules or suppositories. Artemether is formulated in peanut oil, and arteether semams seed oil, for intramuscular injection, and in capsules or tablets for oral use. The artesulate is formulated either as tablets, in a gel placed in a gel for rectal administration (called rectofen™) or as a dry powder for injection of artilic acid supplied with an ampoule of 5 per cent sodium bicarbonate. The powder is dissolved in sodium bicarbonate to form sodium artesuate and then diluted with 5 per cent dextrose or saline for intravenous or intramuscular injection. Artelic acid is a water-soluble second generation compound at the long-term development stage. It has not yet been used for treatment. Most clinical data refer to the most widely used derivative, artesunate. Artemisinin was first isolated from the stems, leaves, and flowers of Artemisia annua by Chinese scientists (Anonymous, 1982; Klayman et al., 1984), but no information on the process was omitted. Researchers at the Walter Reed Army Medical Research Institute (WRAIR) successfully isolated artemisinin derivatives from air-dried parts of plants growing in the wild near Washington, D.C. through oil ether extraction (Klayman, 1985). The plant grows easily in temperate areas and has become naturalized in many countries. It can reach a height of two meters or more, appearing as erect a sample with a wood stem. Artemisinin accumulates in all parts of A. annua except for roots (Abdin et al., 2003). Artemisinin content in donations is 4-5 times larger than the pages. The plant age correlates with the crop of artemisinin, possibly due to a gradual increase in leaf yield and artemisinin content with plant growth. In the agricultural environment in Asia, the production of artesunate has ranged from 5 kg/ha to 50 kg/hectare (Personal Communication, J-M. Kindermans, Médecins Sans Frontières, February 2004). The chemical structure of Artemisinin is unlike other known antimalarials. This includes the endoperoxide bridge necessary for its antimalarials (Brossi et al., 1988). Artemisinin treatment of membranes, especially in the presence of heme, causes lipid peroxidation (Scott et al., 1989; p. 263. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/1101 ×7 Berman and Adams, 1997); this side effect may occur due to drug interactions with intracellular heme or iron (Meshnick et al., 1991). As for the direct effects of artemisinin on the malaria parasite, recent work suggests that artemisinin specifically inhibits PfATP6, SERCA orthologist Plasmodium falm, calcium ATPase (Eckstein-Ludwig et al., 2003). In vivo, artemisinins kill malaria parasites within a host of red blood cells, then dead parasites are spleen, leaving previously infected red blood cells intact and circulating (Chotivanich et al., 2000). It is not yet clear which asexual parasite life cycle stages are very sensitive to artemisinin derivatives: late rings and early trophozoites (ter Kuile et al., 1993) against trophozoites (Geary et al., 1989). However, there is a clear consensus that artemisinin derivatives kill early-stage gametocytes and are more active in the wider range of parasite life cycles than any other antimalarial medicines currently in use. More randomized clinical trials have been published regarding the effects of artemisinins than any other individual or class of antimalarial drugs (Myint et al., 2004). The pharmacodynamic effects of Artemisininins are due to their rapid absorption and activity against many stages of the malaria life cycle, from new aborn forms (rings) to early sexual forms (gametocytes) (Kumar and Zheng, 1990). Their half-life is short (<1 hour artesunate), which protects them from resistance. They reduce the transport of gametocytes, thereby reducing infectivity after treatment, as evidenced by the dramatic collapse of malaria transmission on the Thai-Burmese border (Price et al., 1996; Nosten et al., 2000). Tolerance of the drug is excellent (White and Olliaro, 1998). When used alone, artemisinin derivatives require at least 7 days of treatment. When combined with other drugs, however, artemisinin combination therapy (ACTs) given in 3-day regimens can eradicate the parasite quickly and protect against resistance to both drugs. In addition, artemisinin derivatives are the only first-line malaria treatments to handle gametocytes (early stage). On 20 February 2002, the World Health Organisation (WHO) published a statement calling for governments to ... [for malaria]. The aim is to ensure effective treatment of malaria and to slow down the spread of drug resistance. ... In particular, the WHO recommends the use of artemisinin-based combination therapy (WHO, 2001). p. 264. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × With the largest randomized controlled trials ever conducted in antimalarials in Africa, significant levels of evidence have now been gathered to suggest that artemisinin-based combinations improve cure rates, reduce gametoc carriage, and are well tolerated with some serious adverse effects. In the first of these multicentre studies, 941 children with uncomplicated P. falciparum malaria were randomised to 3-day treatment with amodiaquin plus artesunatem or amodiaquin plus placebo. Both schemes were well tolerated. The combination of arrest and amodiaquin significantly improved treatment efficacy in the Gabonese group (85 versus 71%, p=0.02) and Kenya (68 vs. 41 percent, p<0.0001). In Senegal, however, two regimens were equivalent: the day-28 cure rates for amodiaquine-artesunate versus amodiaquine were 82, compared with 79 percent (p = 0.5) (Adjuik et al., 2002). The efficacy and safety of the combination of artesunate and sulfadoksin-pyrimemamine (SP) has been evaluated in randomised controlled trials in 2,865 patients in sub-Saharan Africa. The results of the first study in Gambia (von Seidlein et al., 2000) (where the incidence of treatment with SP monotherapy was 93 percent) showed that both the incidence of cure and parasite clearance was significantly higher in patients who received 3 days of artesunate plus a single dose of SP compared to patients who received SP alone. Gametoc carriage was 68 percent followinga solo SP treatment, compared to 21 percent after the artesunate-SP combination (p= 0.001). By contrast, underlying SP resistance in Uganda led to unacceptable late recedation rates when artesunate-SP was used there (Dorsey et al., 2002). This conclusion emphasizes that combining artemisinin with longer-acting drugs without basic resistance may prove to be the optimal mode in many areas. On the other hand, in Thailand, where drug resistance is particularly severe, artesunate plus meffoquine was very effective, even in areas where mefloquine resistance was previously quite common (Price et al., 1997). In the largest therapeutic efficacy study with AKT, artesunate plus mefliline produced a long-term, increased cure rate (almost 100 percent from 1998), despite the established resistance to only high doses of meffoquine observed between 1990 and 1994 (Nosten et al., 2000). Cure rates with other ACTs (atovaquone-proguanil-artesunate, artemether-lumefantrine) in Asia are also consistently above 90 percent (van Vugt et al., 1998, 1999). Coartem (artemether-lumefantrine) is the first fixed-dose ACT, with Page 265 Share Cite Recommended quote: 9 Antimalarial drugs and drug resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. Coartem is effective against all P. falciparum and very well tolerated when used in a six-dose regimen over 3 days. Coartem's main drawback is its twice-daily eating and lumefantrine variable absorption associated with dietary fat intake (if patients are unable to eat, or consume a very low fat diet while taking the drug, low cure rates can be caused). In randomized studies comparing the six-dose regimen of oral artemether-lumefantrine with meflovin-artesulate multi-resistant P. falciparumalarium, artemether-lumefantrine was equally effective (94-100 percent) and generally better tolerated than mefloline-artesunate (van Vugt et al., 1999, 2000; Lefevre et al., 2001). Arteuate can be used injection or as a rectal candle. When comparing intravenous artesunate and quinine in 113 adults with severe malaria, mortality with artesulate was observed in 12 percent and 22 percent with quinine (p=0.22) (Newton and al., 2003). In hyperparastic patients who had no other severe malaria effects but who were at increased risk of developing severe malaria, oral arrest was found to be superior to intravenous quinine, reducing both clinical symptoms and parasites (Luxemburger et al., 1995). Rectally administered artesin has been shown to be safe and very effective in children and adults with uncomplicated to moderate falciparum malaria (Sabchareon et al., 1998; Karunajeewa et al., 2003; Barnes et al., 2004). Several recent randomised controlled and open-label studies on rectal artesunate in Africa and Asia have shown that the efficacy of single-dose single-dose single-dose rectal artesunate (10 mg/kg) in moderately high-end falciparium in both children and adults has rapidly demonstrated antimalarial efficacy in both children and adults prior to final treatment. All patients had evidence of adequate absorption of the drug. The clearance of malaria parasites from peripheral blood with rectal arrest was consistently faster than with quinine injection. There are also several small open-label studies, some of which were randomized to demonstrate clinical and parasitological efficacy of rectal arrest in adults with severe P. falciparum infections (Awad et al., 2003), where rectal aratroate was re-administered, and in combination with a second oral antimarzine to prevent recrudcence. These clinical and parasitic responses suggest that rectal artea may prove to be very beneficial for initial treatment in acute malaria patients who are unable to take the drug orally (and for whom parenteral medicines are not immediately available due to limited local resources). In Ghana, artesunate suppositories have already been given to trained village volunteers; In the future, traditional healers could also have Page 266 Share Cite Suggested Quote: 9 Antimalarial Drugs and Drug Resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. If used extensively enough, rectal artesunate could have a major impact on malaria death in Africa. In the early 1970s, Chinese scientists described the antimalarial properties of artemisinins and their excellent tolerability and safety (Anonymous, 1982; Luo and Shen, 1987). Further review in published and unpublished studies on arteminisinin derivatives confirmed previous Chinese findings (Pukrittayakamee al., 2000). These adverse reactions reported have been reported specifically related to one form or route of administration of artemisinin. Neutropenia (but not agranulocytosis) and asymptomatic ECG abnormalities occurred in 1.3% of patients; decreased reticulate count, anaemia, eosinophilia and increased aspartate aminotransferase (liver enzyme) occurred in ≤ 1.0% (Taylor and White, 2004). In Western Thailand, Price and colleagues (1999a) conducted a detailed study of oral artesunate or artemether used alone or in combination with mefliline. Artemisinin derivatives were associated with significantly lower adverse reactions than mefliline-containing regimens: acute nausea (16 vs. 31 percent), vomiting (11 to 24 percent), anorexia (34 versus 52 percent) and dizziness (15 vs. 47%). Oral artesulate or artemether alone was well tolerated. As these data were published in two cases of acute urticaria and anaphylaxis that occurred in the same population after anaesthetate monotherapy, increasing the total number of allergic reactions in 6 patients from approximately 17,000 or 1 in 2,833 (Leonardi et al., 2001). Experience with Coartem is growing rapidly. In large-scale clinical trials, the combination was very well tolerated, regardless of whether it was used as a four- or six-dose regimen. Coartem has been better tolerated than mefloquine monotherapy or arrested plus meffoquina (van Vugt et al., 1998; Looareesuwan et al., 1999). The reported side effects are usually mild, including Page 267 Share Cite Suggested Quote: 9 Antimalarial Drugs and Drug Resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. Detailed prospective studies do not indicate cardiotoxicity (van Vugt et al., 1999; Bindschedler et al., 2000). Twenty severe side effects in 1,869 patients are 19, which could be explained based on a malaria episode or concomitant disease; artemether-lumefantrine may have contributed to the development of hemolytic anemia in one 35-year-old patient 13 days after discontinuation of the drug (Bakshi et al., 2000). Dogs receiving high doses of intramuscular artemether or arteether have developed a specific selective brain stem damage model, especially in connection with reticular formation, vestibular nuclei and nuclei associated with the auditory system. Clinical signs included gait disturbances; loss of reflexes in back and pain reactions; significant loss of the brain stem and eye reflexes; cardiorespiratory depression; and death. ECG changes included QTc interval prolongation and strange changes in the ST-T segment (Brewer et al., 1994). A similar selective brain pathology pattern was also found in mice, rats and Rèze monkeys 1998; Petras et al., 2000). In mice, parenteral artemether was more neurotoxic than artesulate, resulting in exacerbated, irreversible neurological deficits that include balance, and death by increasing doses (Nontprasert et al., 1998). Recent studies have shown that neurotoxicity is determined by the pharmacokinetic properties of the medicinal product. Long-term CNS exposure, which is significantly more neurotoxic than intermittent short-term exposure through slow absorbing or excreted artemisins. Thus, the intramuscular artemether and arteether are more neurotoxic in experimental animals than the same medications given orally, or artesunate given in any way. One case report so far has described acute cerebellar dysfunction, including slurred speech, ataxia, impaired heel lower leg movements, and dysdiadochokinesis after treatment of falciparum malaria with oral arrest (Miller and Panosian, 1997). Detailed neurological data from Price and colleagues (1999a) include neurological tests performed on nearly 2,000 children older than 5 at the beginning, and on days 2, 7 and 28 after treatment, with artemether only, artesunate only, or artesunate plus meflinate. Small-course therapy with artemisinins alone or in combination with mefliline was associated with a self-limiting, small neurological deficiency in a minority (<1 percent) of patients in the first days of falciparum malaria. p. 268. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × In a recent case control study in 150 patients with uncomplicated malaria receiving artemether-lumefantrine, a slight decrease in auditory acuity was observed compared to age-consistent healthy controls (Toovey and Jamieson, 2004). In contrast, 242 Vietnamese patients who received up to 21 doses of artemisinin or artesunate treatment showed no differences in audiometry or hearing treatment compared to 108 age and site-appropriate controls (Kissinger et al., 2000) or 79 Karen patients receiving two or more artemethether or test therapy doses compared to 79 age and site-coordinated controls (van Vugt et al., 2000). Most recently, neuropathological brain stem evaluations were carried out in patients who died of severe falsification after treatment with high intramuscular artemether doses (doses higher than normal) (Hien et al., 2003), revealing lesions similar to those observed in experimental animals. Together with the cumulative body of negative clinical data, including detailed studies of audiometry and hearing-induced potential in patients who received multiple courses of artemisinin derivatives of uncomplicated malaria, as well as high doses of artemether severe malaria (Hien et al., 1996) - evidence weight suggests that neurotoxicity animals do not occur in humans receiving the current recommended doses of treatment. The widespread use of water-soluble compounds (which are less neurotoxic) rather than injected oil derivatives in animal models increases the additional safety margin. Published data on the treatment of malaria during pregnancy with artemisinin derivatives are derived from China (Li et al., 1990), the Thai and Burmese border (where the highest use is) (McGready et al., 1998, 2000, 2001) and Gambia (Deen et al., 2001). Chinese data describe 23 women treated with artemether or artemisinine at weeks 17 to 38 who did not show any evidence of foetal or maternal toxicity. Published experience with artemisinin in pregnant women in Thailand includes observational data on 461 cases with an arrest (n=528) or artemether (n=11) in 539 cases of acute P. falciparum malaria, including 44 episodes in the first trimester. The number of Thai women treated with artemisinin was comparable to the community rates for abortion, stillbirths, congenital malformations and/or mean geturition periods during childbirth. All newborns who were observed for 1 year developed normally, including those who were exposed to artemisinin during the first trimester of pregnancy Page 269 Share Cite Suggested Citation:9 Antimalarial Drugs and Drug Resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × (McGready et al., 2001). In another study involving 287 pregnant gambia women unintentionally treated (during mass dosing) with one dose of artesunate plus SP during the first, second or third trimester of pregnancy, there was no evidence of obstetric or foetal toxicity compared to women who were not exposed to artesatic plus SP (Deen et al., 2001). No data have been published on the use of artemether-lumefantrine in pregnant or breast-feeding women. Studies investigating the potential risk of artemisinins during the first trimester of pregnancy (when birth defects are most likely) were also conducted in laboratory animals. In 2001, a WHO report concluded: Preclinical studies have consistently shown that artemisinin and its derivatives do not show mutagenic or teratogenic activity, but all of these drugs caused foetal resorption in rodents at relatively low doses (WHO, 2001). More recently, in some experiments in rats and rabbits, but not in others, doses of artemisine similar to humans were administered to pregnant animals. For this reason, in 2002, the WHO convened two more expert meetings to review animal and human evidence relating to the use of artemisininins in pregnant women, concluding: Overall, current data are encouraging, but more safety data on artemisinin derivatives are needed to support the use of artemisininins in pregnant women with uncomplicated malaria. although no data have been published on the treatment of severe malaria during pregnancy with artesunate or artemether, these drugs have been widely used and have been found to be effective. In particular, artesunate and artemether often prefer more than quinine and quinidine during pregnancy because they do not cause hypoglycemia and are easier to enter (Tran et al., 1996). However, if ACTs are widely introduced, tens of thousands of pregnant African women include- Page 270 Share Cite Recommended Quote: 9 Antimalarial Drugs and Drug Resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. The use of Artemisinins in pregnant women, especially in the first trimester, is an issue that is, appropriately, receiving constant attention from the international supervisory authorities. At national level, pharmacovigilance programs will be required to track the various effects caused by artemisinins, as well as new ACT partner drugs throughout pregnancy. For example, mefloquien given at any stage of pregnancy in Thailand is associated with a four-fold increase in stillbirths (Nosten et al., 1999), but the same effect was not observed in pregnant women treated with mefliline in Malawi (Steketee et al., 1996). This conclusion also requires further action. Although not every factor responsible for the emergence and spread of parasitic resistance is fully known, it is clear that antimalarial resistance may develop in anti-almalrium drugs and that drug pressure is a key prerequisite. Other important respondents are the elimination half-life of the medicinal product, the biomass of parasites and the rate of malaria transmission (Talisuna et al., 2004). The appearance of drug-resistant organisms can be considered in two discrete stages: in the case of initial de novo (rare genetic phenomenon) which first produces a resistant mutant, and then a selection process leading to its preferential transmission and spread. Resistance arises from spontaneous mutations or gene duplication, which are independent of drug pressure. When formed, however, resistant

mutants have survival benefits in the presence of antimalarial drugs and, on the contrary, lack of survival in the absence of at least some antimalarial drugs. The resulting fitness costs may lead to a decrease in the prevalence of resistance after the drug pressure has been eliminated (this model has been shown to be resistant to chloroquine in Malawi [Kublin et al., 2003], although the significance of its action remains unclear). Factors influencing the development of resistance are: parasite mutation rate, degree of resistance due to genetic changes, cost of suitability of the resistance mechanism, proportion of transmissive infections exposed to all drugs, drug concentration profile, (e.g. dosing, duration, adherence) and society (e.g. quality, availability, distribution) patterns of drug use and profile of community immunity (White, 1999). The possible role of the mass drug administration in accelerating the emergence of antimalarial resistance was first highlighted by Payne (Payne, Page 271 Share Cite Recommended citation:9 Antimalarial Drug and Drug Resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 × 1988), who observed that chloroquin resistance had one common de ass in different locations: long-term, local use of chloroquine for treatment. Subsequent studies in the coastal states of Kenya, Malawi, Mali and Bolivia revealed a positive correlation between drug use and the prevalence of in vitro parasite resistance or resistance-related mutations (Diourte et al., 1999; Nzila et al., 2000). A recent study in Uganda showed that the prevalence of chloroquine resistance was higher in areas with high frequency chloroquine administration, as reflected in detectable chloroquinometabolics in urine (Talisuna et al., 2002b). However, SP resistance was highest in high-transmission sites with relatively low use of SP, suggesting that factors in addition to drug pressure influence the spread of SP resistance to the drug. The role of the elimination half-life of the drug in the development of parasitic resistance has recently been reviewed and modelled (Hastings et al., 2002). Drugs with long elimination phases are essentially selective filters that allow infection with resistant parasites to flourish, while residual drug levels suppress infectious-sensitive parasites (Watkins and Mosobo, 1993). Slowly eliminated drugs, such as mefliline (T 1/2=3 weeks) provide such a filter for months after administration of the drug. As a result, the selection pressure can be enormous. In Kenya, strong selective sp resistance pressures were found to work even under conditions of supervised drug use and optimal dosing of SP (Watkins and Mosobo, 1993). Plasmodium falciparum infections occurn between days 15 and 52 after SP treatment had a higher likelihood of pyrimemamine resistance in vitro. Selective pressure on home-based use of SP (in line with who's strategy for home management of the fever) could accelerate the emergence of SP resistance to an even greater degree (Talisuna et al., 2004). Finally, drug-resistant mutant parasites are statistically more likely to get out of infections associated with a high number of parasites. Such major parasite biomas infections are more common in non-immune individuals, as evidenced by a higher prevalence of chloroquinotripressent infections, and chloroquine treatment failures observed in African children compared to adults (Dorsey et al., 2000; Djimde et al., 2001; Talisuna et al., 2002a). Non-inmuniform patients infected with a high number of parasites receiving inadequate treatment with poor quality of medicine, oral .c.) is another strong source of resistance. This emphasizes the importance of correct prescribing and good adherence to certain drug regimens, slowing the emergence of resistance. Re-transmission and further transmission of the de novo-resistant malaria parasite is essential during the spread of resistance. Killing transmis-Page 272 Share Cite Suggested Quote: 9 Antimalarial Drugs and Drug Resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. Gametocs carrying resistance genes bore transmission intensity while resistant biomass has expanded to numbers causing disease (>107 parasites) (Jeffery and Eyles, 1955). In order to reduce the spread of resistance, the production of gametocytes from recrudescences resistant infections should be prevented. One way to look at the relationship between resistance and transmission intensity is as follows. In low-transmission areas, most malaria is symptomatic, and therefore the choice occurs at a time when a relatively large number of parasites in a particular individual encounter antimalarial drugs. However, in larger transmission areas, symptomatic disease usually occurs during the first years of life. Later, malaria becomes less symptomatic due to incomplete immunity (sometimes referred to as pre-treatment), which keeps the infection below the symptom threshold. Despite premunisation, many people in high-transmission areas still receive antimalarial treatment throughout their lives, often inappropriately. Fortunately, most treatments are largely unrelated to parasitemia peaks, thereby reducing the selection of resistant strains. Immunity also reduces the occurrence of resistance significantly (White and Pongtavornpinyo, 2003). Even if a resistant mutant does not survive and multiply, the probability that it will produce sufficient gametocytes for transmission is reduced by the presence of other competing parasite genotypes (Dye and Williams, 1997). Since significant symptoms usually apply only to young children in high-transmission areas, the fact that children make up only 20 percent of the population roughly, and their blood volume is much lower than in adults (therefore containing less common parasites) is the final limitations on the emergence of drug resistance in such areas. The net result is generally a significant reduction in the probability of de novo selection and subsequent resusergent parasite transmission in high and low transmission areas, as confirmed by the historical emergence of chloroquine resistance and a faster increase in antifola resistance in low Page 3 273 Share Cite Suggested Quote: 9 Antimalarial Drugs and Drug Resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × the historical occurrence of drug-resistant P. falciparum is reviewed elsewhere in this report (see Chapter 5). The following is a brief summary of the current levels of overall resistance to chloroquine and SP based on an in vivo therapeutic treatment failure (TTF) assessment. Data showing resistance in vivo to chloroquine and SP in Africa are also provided in maps (Figures 9-1 and 9-2). In Africa, the median chloroquine (CQ)-TTF for children under 5 years of age exceeded critical values (TTF=25 percent) in all eastern/large lake (seven) and central/south (four out of four) regions. However, in West Africa, only one of the five countries had an average CQ-TTF higher than the critical value. The median CQ-PF in Southeast Asia ranged from 38 to 91%, from 23 to 38 FIGURE 9-1 In vivo resistance to chloroquine in selected countries, sub-Saharan Africa, 1996-2002 (average range). PF = parasitologic failure; CF = clinical failure. SOURCE: From Talisuna et al. (2004); Kazadi et al. P. 274. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. Date dates in the upper-right corner; PF = parasitologic failure; CF = clinical failure. The median (range) given. Superscript numbers by range = number of studies contributing to data; duration of follow-up in days. SOURCE: From Talisuna et al. (2004); Kazadi et al. (2003); Plowe et al. (2004); Unpublished data from the CDC. percent in the Pacific, between 46 and 77 percent in the Indian subcontinent and between 12 and 69 percent in the Middle East. In South America, the lowest average CQ-PF was 33 percent, and the highest was 50 percent, while the corresponding lowest and highest estimates for CQ-TTF were 44 and 100 percent, respectively. In Africa, the mean SP-TTF ranged from 0 to 35 percent, and the mean parasitological failure (SP-PF) ranged from 0 to 76 percent. In Asia, SP-TTF ranged from 9 to 35 percent, and in South America it ranged from 3 to 32 percent. SP-PF was higher and ranged from 5 to 67 percent in Asia, and between 6 and 20 percent in South America. Overall, these recent data suggest a high prevalence of CQ resistance (TTF>25 per cent) in eastern/large lakes and central/southern regions where SP resistance occurs. This situation could be Page 275 Share Cite Suggested Quote: 9 Antimalarial Drugs and Drug Resistance. Institute of Medicine. 2004. Lives, Buying Time: The Economy of Malaria Drug-Era Resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. Currently, although the laboratory has acquired strains of P. falciparum (Inselburg, 1985) and Plasmodium yoelii (Peters and Robinson, 1999), there is no clinically relevant resistance to artemisinin. The clinical and laboratory strains of P. falciparum may also vary in vitro (Le Bras and Durand, 2003) without clinical effect. Two patients infected with P. falciparum who failed arrest therapy had parasites that were later shown to be susceptible to artemisinin in vitro (Luxemburger et al., 1998). In general, recrudescence after artemisinin monotherapy is due to host factors (e.g. drug metabolism) rather than failure due to parasite resistance. If there is no functioning spleen, dead intraerythrocytic malaria parasites are not removed. The persistence of these parasites on blood smears indicating delayed clearance may be misinterpreted as artemisinin resistance (Chotivanich et al., 2002). However, even if 7-day courses of artemisinin derivatives are given, cure rates usually do not exceed 90-95 percent. This inability to cure all patients with artemisinin does not reflect resistance per se, but a curious phenomenon in which a very young parasite subpopulation remains arrested in a state of development for more than a week after treatment (Personal Communication, D. Kyle, 1997). These parasites can later multiply and cause my bill. However, recrudescent parasites are no more resistant to artemisinin than primary infection (White, 1998). Multi-resistant P. falciparum (with MDR enhancement) is more resistant to the use of artemisinin than non-MDR parasites, but differences do not affect therapeutic results. However, they have led to incorrect assumptions about the choice of resistance (Wongsrichanalai et al., 1999). For example, on the western border of Thailand, when mefliline resistance deteriorates, in vitro susceptibility to dihydroarteminin (the main metabolite of artesunate and artemether) was also decreased. However, after systemic administration of meflixin-arteusate, the region's full efficacy of artemisinin was restored with the efficacy of mefliline (Brockman et al., 2000). Plasmodium vivax It was only 1989-30 years after chloroquine resistance first appeared P. falmcipa-ka chlorquino-resistant strain P. vivax Page 276 Share Cite Suggested quote:9 Antimalarial drugs and drug resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. Chloroquinoqua-resistant P. vivax (CRPV) infections were subsequently from Indonesia-New Guinea (Baird et al., 1996; Fryauff et al., 1998), Burma (Marlar-Than et al., 1995), India (Garg et al., 1995) and Guyana (Phillips et al., 1996). Sporadic CRPV infections are now visible in many geographical regions of the world, but are not increasing in most regions (Mendis et al., 2001). One exception is eastern Indonesia, where the risk of therapeutic failure after chloroquine approached 80 percent 28 days after treatment (Baird et al., 1997). Fortunately, drug-sensitive parasites P. vivax are at little disadvantage in relation to drug-resistant strains, mainly because P. vivax gametocytes develop quickly in the blood of infected individuals, and they have less drug exposure than P. falciparum before shipment. Among the plasmodium species that infect humans, only P. vivax and P. ovale have latent liver hypnozotic, which can cause clinical relapse of malaria after successful eradication of circulatory parasites. Although primaquine, an 8-aminoquinoline drug, has been used for decades to prevent relapse, some P. vivax and P. ovale infections, acquired in Southeast Asia and the SouthWestern Pacific region, are now tolerant of its effects. As a result, the new recommended adult dose of primaquine is 30 mg of the base drug per day for 14 days (420 mg total dose) compared to the previous 15 mg daily dose over the same period. The alternative regimen for primary emlerified infections is the use of 45 mg PQ once weekly for 8 weeks. This approach reduces the likelihood of primaquine producing hemolysis in patients with mild G6PD deficiency while improving its effectiveness against tolerant strains. The use of primaquine should be avoided strictly in patients with severe G6PD deficiency. Four methods are currently available to investigate or measure the efficacy of antimalarials against drug resistance: in vivo, in vitro, animal model studies and molecular markers (Bloland, 2001). Of all the available methods, in vivo tests most accurately predict the likelihood that parasites that infect the target human population will respond to a specific treatment regimen. In vivo testing process involves monitoring malaria infected individuals after administration of certain doses Page 277 Share Cite Recommended quote: 9 Antimalarial Drug and Drug Resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/× 11017 In 1973, the World Health Organization established criteria for the evaluation of chloroquino and amodiaquin and recommended a 28-day observation period. These protocols provided that patients would remain screened for 28 days to avoid re-infection during the evaluation period. The initial WHO definitions of in vivo drug sensitivity (sensitive [S] and progressively deteriorating levels of resistance [R1, R2 and R3]) are shown in Tables 9 to 3. The original protocols were used until 1990, when a shorter duration of follow-up (typically 14 days) was recommended, especially in areas with high transmission, while some research groups adopted longer observation periods (up to 63 days) when evaluating slowly eliminated antimalarial drugs. Shorter follow-up periods in the assessment of antimalarial treatment often underestimate drug-resistant recrudescence infections, which, even in high-stable transmission areas, lead to significant morbidity, especially anaemia. The WHO modified protocol with a shortened observation period (WHO, 1996) highlighted clinical results on parasitological outcomes, recognising that clinical parameters are equally important indicators of treatment response. The last protocol of 2003 was developed with the specific objective of unified testing worldwide under a common methodology and classification scheme. In this scheme, parasitic failure was brought back into the classification scheme, recognising that even externally asymptomatic parasites have adverse health consequences (Price et al., 2001). In all areas, regardless of the intensity of malaria transmission, assessment 9-3 TABLE Initial WHO classification in Vivo Antimalarial drug sensitivity S (sensitive) Reduction to <25% from baseline parasitemia on Day 2 with smear negative malaria from day 7 to the end of observation (28 days, or longer than the drug with long half-life, eg mefliline) R1 response Baseline parasitic clearance, negative smear on Day 7 followed by a repeated decrease of 8 days or more after treatment R2 response Baseline clearance or significant parasitic decrease (<2 5% of the initial number on Day 2), but with persistence or recedcence parasitemia daily 4-7 R3 Response There is no significant reduction in parasitemia SOURCE: Bruce-Chwatt et al. (198 paragraph 5). p. 278. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/1101 ×7 doi: 10.17226/11017. The justification for this requirement is that even in populations with low acquired immunity (as in areas with low or very seasonal malaria transmission), younger children tend to have a less favourable therapeutic response to antimalarials than older children and adults (ter Kuile et al., 1995). Baseline parasite density suitable for incorporation in in vivo tests between 1000 and 100 000 nonexex-free parasites/uL in low to moderate transmission areas and between 2000 and 200 000 non-sexual parasites/uL in high transmission areas, as confirmed by the currently accepted definition of hyperparasimic (WHO, 2000) (column 9-1). In vivo methods usually underestimate the true number of treatment failures and therefore underestimate the level of antimalarial medicines. The reasons for this are: in areas of medium and high transmission, older children and adults have significant antiparasitic immunity. This leads to a high probability of self cure giving a false impression of the effectiveness of the drug. Short-term (<14 days) further assessments have not prevented unsuccessful treatments. In a recent review of more than 16,000 patients, followed by 28 days in the treatment groups from 1990 to 2003, the widely used 14th-day assessment did not match 63 to 100 percent of all treatment failures and did not have a natural failure assessment; The 28-day assessment missed one third of the unsuccessful treatment, but was expected to have a value for the overall treatment rate (Stepniewska et al., press). In vitro tests for antimalarial drug resistance are analogous to antibiotic susceptibility tests conducted in hospital and commercial microbiology laboratories. In short, malaria parasites derived from venous blood samples are commonly cultivated microtitrition wells with a known concentration of antimalarial drugs. The effect of the medicinal product is then quantified according to the ability of the product concerned to inhibit the growth or maturation of parasites schizonts (Rieckmann et al., 1978). In vitro tests are useful because they allow multiple tests (including new and experimental drug panels) with individual blood isolates. However, their results often differ from in vivo tests, as the latter are influenced by several host factors, mainly immunity. Currently, in vitro tests are only used for the susceptibility testing of P. falciparum medicinal products. Their relative expenses, as well as the technical requirements for cultivating fresh blood samples, limit their large-scale use under normal field conditions. p. 279. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × BOX 9-1In Vivo drug efficacy testing, drug selection and malaria treatment policy – 2003 development assessments for in vivo evaluations of the efficacy of malaria medicines are designed to measure treatment success or failure rates in malaria patients who are representative of the higher risk in the area. These assessments assume a relatively small number of patients (preferably at least 50) with slide-approved malaria, treated with a combination of medicines or medicines, and are monitored over time. All treatments are observed to ensure adherence. Patients are observed for relapse or persistence of malaria parasitemia for 14 or 28 days (sometimes longer). Parasites with or without additional clinical symptoms are observed. Patients' response to treatment is classified in early treatment failures (ETFs occurring within 3 days of initiation of treatment), late clinical failure (LCF- Relapse of parasites with fever 4 to 28 days), late parasitological failure (LPF, a recurrence of parasites without fever between 4 to 14 days or 28 days), and adequate clinical and parasiological response (ACPR: no parasite recurrence during monitoring). Ideally, a system of control sites (usually between four and eight places) chosen to represent epidemiological, ecological and geographical differences in the country is used to describe the effectiveness of treatment in the country. Data from these checklists are used to inform the development of malaria drug policy and/or national guidelines for the treatment of malaria. These data determine when a particular malaria treatment can no longer be considered effective and should therefore no longer be used in a national malaria treatment policy. In areas with high transmission intensity in sub-Saharan Africa, the WHO recommends reducing the total clinical failure by more than 15% (ETF + SFK) and more than 25% of parasitolo failure (LPF) within 14 days (WHO, 2003). However, there are no clear recommendations on how to reconcile conflicting data from different control sites (i.e. if the policy were to be changed if one of the eight sites demonstrated high failures, when all eight are, or for some time at the same time?). In any case, since the change and implementation of a new treatment policy takes time before the process achieved at these levels must be initiated. In many cases, the programmes have waited too long to initiate change, and the level of resistance is much higher until new drugs are used. Recent advances in molecular biology, in particular the use of polymerase chain reaction (PCR), have made it possible to characterise a number of markers of genetic resistance to the drug P. falciparum (Greenwood, 2002; Wongsrichanalai et al., 2002). Currently, attention is focused on four drug resistance genes (Wernsdorfer and Noedl, 2003). The main genes that determine resistance to the antifola drug pyrimemamine and sulfadoxin are the dihydrofolate rejuctasis gene (pfdhfr) and dichopteroate sinsa-Page 280 Share Cite Suggested quote: 9 Antimalarial drugs and drug resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/1101 ×7 (pfdhps). High levels of pyrimethamine resistance result from the accumulation of mutations in the DHFR gene, mainly in codons 108, 59, 51 and 164 (Plowe et al., 1997; Wang et al., 1997); quadruple mutants combining all four-point mutations confer the most serious resistance (Wongsrichanalai et al., 2002). Point mutations in DHPS are associated with reduced sensitivity to sulfaxine in vitro (Wang et al., 1995). Although the exact relationship between dhfr and DHPS gene mutations and clinical SP resistance is unclear, current data suggest that the sensitive dhfr alle predicts SP treatment success regardless of DHPs alle. et al., February 2001). The main factor of chloroquine resistance is the p. falciparum chloroquin resistance transporter (pfcrt), located on chromosome 7 and encoded by the digestive vacuole transmembrane protein PfCRT (Wellems et al., 1991; Djimde et al., 2001). Although many polymorphism associated with chloroquinos resistance has been identified, the replacement of lysine with lysine in codot in 76 clearly correlates with in vitro resistance in P. falciparum isolates from Africa, South America, Asia and Papua New Guinea (Fidock et al., 2000; Djimde et al., 2001). The same finding is confirmed by an additional in vitro study on different geographical origins (Durand et al., 2001) as well as mali (Djimde et al., Cameroon (Basco and Ringwald, 2001), Sudan (Babiker et al., 2001), Mozambique (Mayor et al., 2001), Laos (Pillai et al., 2001), Thailand (Chen et al., 2001) and Brazil (Vieira et al., 2001). Paradoxically, although cumulative data suggest that a Thr76 mutation is required for resistant phenotype expression, Thr76 is also less significant in chloroquinosa-sensitive P. falciparum strains, suggesting that other polymorphics or genes contribute to resistance (Wongsrichanalai et al., 2002). Conversely, due to the additional contribution to host immunity, individuals from malaria endemic areas harboring parasites with the Thr76 mutation also had successful treatment results after chloroquine (Djimde et al., 2001). The fourth gene, known as P. falciparum multi-drug resistance gene (pfmdr), encodes the transmemebran protein P-glycoprotetine homologous 1 (Pgh1) and modulates the resistance phenotype for some, if not all, of PfCRT mutant parasites. (Wongsrichanalai et al., 2002). Aspartic acid against tyrosine point mutation in codeon 86 has been positively associated with chloroquine resistance in Mali (Djimde et al., 2001), The Gambia (von Seidlein et al., 1997), Sudan (Babiker et al., 2001), Uganda (Flueck et al., 2000), Thailand (Price et al., 1999b) and Brazil (Zalis et al., 1998); however, the same mutation was not associated with chlorquin resistance in other studies conducted in Uganda (Dorsey et al., 2001), Laos (Pillai et al., 2001), Thailand (Chaiyaroj et al., 1999) and Brazil (Povoa et al., 1998). p. 281. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × The relationship between mefliline sensitivity and pfmdr1 gene mutations and/or over-expression was also unclear until studies in Thailand showed an increase in Pfmdr1 (increased number of copies) as the main determining factor for mefliline resistance (Price u.c. In general, although molecular markers allow drug resistance samples in a relatively short time, the long-term difficulty of this approach, especially for chloroquine and meffoquin, is to identify the specific mutations that confer resistance. The problem becomes even more difficult when drug resistance results from multiple mutations on one or more genes. Abdin MZ, Israr M, Rehman RU, Jain SK. Artemisinin, a new antimalarial drug: biochemical and molecular approaches to improve production. Planta Medica 69 (4): 289-299. Babiker A, Borrmann S, Brasseur P, Cisse M, Cobelens F, Diallo S, Faucher JF, Garner P, Gikunda S, Kremsner PG, Krishna S, Lell B, Loolpapit M, Matsiegui PB, Missinou MA, Mwanza J, Ntoumi F, Olliaro P, Osimbo P, Rezbach, Some E Taylor, 2002. Amodiaquine-artesunate against amodiaquin uncomplicated Plasmodium falciparum malaria in African children: Randomized, multicentre study. Lancet 359(9315):1365-1372. 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CHLORIN IS a derivative of quinine 4-aminoquinoline first synthesized in 1934. It is safe for infants and pregnant women, and was a historical drug of choice for treating nonsevere or uncomplicated malaria and to prevent malaria in travelers. Chloroquine acts mainly against the aborn stages of the bloodthirsco, although it also acts against the circulatory stage of infectious mosquitoes. Due to the widespread resistance to the drug, its usefulness is increasingly limited. Side effects are uncommon and usually mild. AMODIAQUINE, which is closely related to chloroquine, fell out of favor because it had adverse effects on the bone marrow and liver when used for prevention. Amodiaquine is currently being reused as a co-formulation partner with artesunate. There are concerns about toxicity. ANTIFOL COMBINATION DRUGS include various combinations of dihydrofolate reductase inhibitors (proguanil, chlorproguanil, pyrimethamine, and trimethoprim) and sulfaamide drugs (dapsone, sulphafen, sulfamethoxazole, sulfoxine, and others). Partner drugs antifol combinations have similar mechanisms of action; they do not thus protect each other from resistance to the same extent as unrelated medicinal products. Current combinations include sulphadoxine-pyrimamine (SP; sulphafen/pyrimethamine (Metakelfin) and sulfamethoxazole/trimethoprim (comicoxazole). Proguanil has also been used in combination with chloroquine for the prevention of areas with moderate chloroquine resistance, although it only confers minimal additional benefits, especially with long-term effects page 292 Share Cite Recommended Citation: 9 Antirialmala drugs and drug resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × (Steffen et al., 1993). When used for prevention, Fansidar can cause severe allergic reactions: in American travelers, Fansidar was associated with severe skin reactions (1 in 5,000 to 8,000 users) and mortality (1 in 11,000 to 25,000 users) (Miller et al., 1986). These negative results are not so common when a single dose of Fansidar is used for treatment. Concerns about the use of sulfaamide drugs during pregnancy outweighs the known risk to the mother and fetus of untreated malaria. The latest combination of antifol is chlorproguanil and dapson, also known as Lapdap. This particular combination is inherently more effective than Fansidar (even in areas where resistance is present) and has a much shorter elimination time, which can reduce the likelihood of resistance (Watkins et al., 1997; Mutabingwa et al., 2001). On the other hand, its shortest half-life requires lapdap to be given more than 3 days instead of a single dose of SP. TETRACIKLINE and its derivatives, such as doxycycline, can be paired with other medicinal products for treatment or used as separate preventive measures. In areas where the efficacy of quinine decreases, tetracyclines are often added to quinine to improve treatment rates. Tetracyclines are also used with abbreviated quintin courses to reduce quinine-related side effects. Tetracyclines are contraindicated in pregnant or breast-feeding women or children under 8 years of age. Common side effects include nausea, vomiting, diarrhoea, secondary yeast infections and photosensitivity. 8-aminoquinoline – privatemineium acts against malaria parasites in the liver, thereby reducing the risk of relapse of P. vivax or P. ovale. Primaquine is also relatively effective (74% efficacy against P. falciparum; 90 percent efficacy against P. vivax) when used for prevention (Baird et al., 1995). Although it also has activity against blood stage asexual parasites, the concentration of drugs that kill fully mature blood parasites is toxic. Primaquine is also a powerful gametocidal drug, i.e. it kills the sexual stage of malaria parasites in infectious mosquitoes. Primaquine may cause severe and potentially fatal haemolytic anaemia in people with glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency. The heaviest Variant B of the Mediterranean and the related Asian variants of the G6PD deficit occur at a high level between several groups and regions: Kurdish Jews (62 percent), Saudi Arabia (13 percent), Burma (20 percent), and (6 percent) and now spread through migration and interuras. The primary should not be used during pregnancy. Tafenoquine, a synthetic primaquine analogue, is currently being tested. It is very effective against both the liver and blood stages of malaria. Due to its long half-life (14 days vs. 6 hours in primaquine), Page 293 Share Cite Recommended Quote: 9 Antimalarial Drugs and Drug Resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. As in primaquine, taphenoquin may cause acute haemolytic anaemia in patients with G6PD deficiency. MEFLOLINE WINE is a quinine quinoline-methanol derivative that can be used for treatment or prevention in most areas with multi-resistant malaria. Resistance to mefliline occurs frequently in parts of Southeast Asia, however, and sporadic resistance has been reported in areas of Africa and South America. Meflovin causes a relatively high incidence of neuropsychiatric adverse reactions when used at the treatment doses and to a lesser extent when used for prophylaxis. In one large study in Asia, meflifin was associated with stillbirth when used during pregnancy (Nosten et al., 1999). HALOFANTRIN is a compound of phenantrūnmetanol with activity against hemorrhages of the malaria parasite. This is especially useful in places where there are many resistant falciparum malaria. Cardiac conduction disorders (especially prolongation of PR and QT intervals on a standard electrocardiogram) are the main deficiency of halofantrine (Nosten et al., 1993). Administration of halofantrine immediately after mefliline or quinine therapy also increases the risk of cardiac complications. Halofantrine and meflixin may have clinical cross-resistance (Wongsrichanalai et al., 1992; ter Kuile et al., 1993). CLINDAMYCIN is an antibiotic with weak antimalarial activity. It should only be used in combination with fast-acting shenzhening ing, e.g. quinine, especially when treating patients with little or no immunity to malaria (Pukrittayakamee et al., 2000b; Parola et al., 2001). Clindamycin is considered safe for use in pregnant women and very young children (Pukrittayakamee et al., 2000a). ARTEMISININ COMPOUNDS includes a compound of artesuin, artemether, artesa and dihydroarteminine derived from the artemisia annua sesquiterpene lactone principle (artemisin). In severe malaria, artemisinin compounds cause faster clearance of parasites and fever loss than quinine. Artemisinins also reverse coma faster than quinine (Taylor et al., 1993; Salako et al., 1994). However, when used separately for a period younger than 5 to 7 days, the recedcence level is high. For nonsevere malaria, artemisinins are most important when used in combination with a second drug (Nosten et al., 1994). Commission 201 meflixin plus 3 days after arrest. The safety of artemisininin in early pregnancy is particularly important as the medicine has caused foetal resorption in experimental animals. Despite conclusive clinical data of over 600 closely followed pregnancy Page 294 Share Cite Recommended Quote: 9 Antimalarial Drugs and Drug Resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. The fixed-dose preparation of Lumefantrine and artemether is sold commercially under the trade name of Coartem or Riamet. Lumefantrine (formerly known as benflumetol) is an antimalarial compound of aryl amino alcohol. Although lumefanthrin does not appear to be chemically related, it does not have the same cardiac exposure as halofantrine (van Vugt et al., 1999). Coartem is marketed in two packs: a six-dose (24 tablet) pack for non-inmunes patients and a four-dose (16 tablet) pack for the use of half-moon patients. While studies do not demonstrate conclusive efficacy of the four-dose regimen in semi-male populations, all patients should receive a six-dose regimen (van Vugt et al., 2000). Lymefantrin is not recommended for use in pregnant women until further safety data are available. ATOVAQUONE PLUS PROGUANIL (MALARONE) is a fixed-dose combination containing 250 mg atovaquone (hydroxynaphthaloquinone) and 100 mg proguanil per adult tablet, which is used daily for prophylaxis. Adult treatment Malarone is 1000 mg atovaquone and 400 mg proguane per day for 3 days. Malaron is also combined with artesunate to treat the uncomplicated multi-resistant falciparum malaria (van Vugt et al., 2002). Malarone is also considered effective in the blood-shaped P. vivax (Looareesuwan et al., 1996a). PYRONARIDINE has been used in China for over 20 years. Although it was reported 100 percent effective in one study in Cameroon, the drug was only 63 to 88 percent effective in Thailand (Ringwald et al., 1996; Looareesuwan et al., 1996b). Further testing is required for the widespread use of pylonidine. PIPERAQUINE is an oral bisquinoline that was discovered in the early 1960s and developed for clinical use in China in 1973. In vitro tests in several laboratories have shown that piperakin roughly reduces the exposure of chloroquine to susceptible parasites and is significantly more effective than chloroquine-resistant P. falciparum. In China, Vietnam and Cambodia, piperacin is now available as a fixed combination with dihydroartemin (it is also combined with trimethoprim and primaquina). Prospective clinical trial data are expected. Page 295: Share the quote suggested in a quote:9 Anti-mealine medicine Drug resistance. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. 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Drug-resistant malaria is considered a major military threat as well as an American public health issue. Military personnel, tourists, consultants, Peace Corps volunteers, and State Department employees traveling to or living in malaria-endemic areas are at risk of disease and death from malaria. When drug-resistant malaria was first encountered by U.S. troops during the Vietnam conflict, the U.S. Army established a malaria research program to develop new preventive and therapeutic drugs for military use, coordinated by the Experimental Therapeutic Division at the Walter Reed Army's Research Center in Washington, D.C. The program was designed to maintain knowledge and laboratory capabilities to manage experimental compounds from a chemist's bench through clinical trials, and to approval by the Food and Drug Administration. WRAIR's achievements are summarised in Tables 10 to 2. Funding for the program peaked at more than $12 million in 1969 (equivalent to about $70 million in 2003, adjusted for inflation) (Figure 10-1), but fell off precipitously when the Vietnam conflict ended. WRAIR's malaria drug development program never closed completely, but public funding began to increase only in the early 1990s (from about $2 million in 1990 to about $14 million in 2004, a constant of 2004 dollars), partly partly the IOM report on malaria research (IOM, 1991) and other favourable reports. Currently, WRAIR has a Department of Defense directive to develop a new malaria prophylactic, and an intravenous artesunate formulation of severe and complex malaria. Perhaps more importantly, WRAIR has become an integral part of the global malaria drug development network, having established strategic alliances with MMV, and the National Institute for Allergy and Infectious Diseases Challenge Grant Program, as well as the pharmaceutical industry. Through MMV projects, WRAIR supports a wide range of page 3 Ndyomugyenyi R, Neema S, Magnussen P. 1998. Use of formal and informal services for prenatal care and treatment of malaria in rural Uganda. Health policy and planning 13(1):94-102. Newton P, Proux S, Green M, Smithuis F, Rozendaal J, Prakongpan S, Chotivanich K, Mayxay M, Looareesuwan S, Farrar J, Nosten F, White NJ. 2001. Fake artesunate in Southeast Asia. Lancet 357(9272):1948-1950. Nshakira N, Kristensen M, Ssali F, Whyte SR. 2002. Appropriate treatment for malaria? Use of antimalarial drugs in children's drucosms in district medical units, drug shops and homes in eastern Uganda. Tropical medicine and international health 7(4):309-316. Nuwaha F. 2002. Popular perception of malaria in Mbarara, Uganda. Tropical medicine and international health 7(5):462-470. Ofori-Adjei D, Arhinful DK. 1996. Impact of training on clinical management of medical assistants in Ghana. Social sciences and medicine 42(8):1169-1176. 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Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017. × HIPC ļoti bezmānijas nabadzīgās valstīs HIV cilvēka imūndeficīta vīrusu HMS hiperreaktīva malārijas splenomegālija HRP-2 histidīna bagāts proteīns 2IDA Starptautiskā attīstības asociācija IFPMA Starptautiskā federācija Farmācijas ražotāju asociācija IMCI Integrēta vadība childhood illness INN International Nonproprietary Name IOM Institute of Medicine (of The National Academies) IPT intermittent preventive treatment IPTc intermittent preventive treatment in children IPTi intermittent profilaktiskā ārstēšana zīdaiņiem IPTp intermitējošs profilaktiskā ārstēšana grūtniecēm IRS iekštelpu atlikušais aerosols ar ITC insekticīdu apstrādāts aizkars ITN insekticīdu apstrādāts (gulta) netkdr notriekt rezistenciLICUS zemu ienākumu valstīm stresamara kartēšanas malārijas risku Āfrikā MDA masu narkotiku administrācijas TAM Tūkstošgades attīstības mērķi MDR multidrug rezistence MEWS malārijas agrīnās brīdināšanas sistēmaMIC minimālā inhibējošā koncentrācija MIM Daudzpusēja iniciatīva par malārijas MMSS malārijas zāles un piegādes pakalpojumu MMV zāles malārijas Venture MoH Veselības ministrijas Veselības MPC minimālā parazitādīda koncentrācija MQ mefloquine MSH Management Sciences veselības MSL Medical Stores Ltd. MSP-1 merozoite virsmas proteīna-1 MTCT mātes uz bērnu transmisijas MVI Malaria Vaccine InitiativeNGO nevalstiskā organizācija NIH National Institutes of Health (USA) Page 5 Page 334 Share Cite's suggested quote: Glossary. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria laikmetā rezistences. Washington, DC: DC: National Academy Press. doi: 10.17226/11017. × Glossary acidosis. imbalance of the body's acid-bases, which contains excessive blood acidity. metabolic acidosis results from excess acid due to abnormal metabolism (as severe malaria), excessive acid intake, renal retention, or excessive bicarbonate loss (as severe diarrhea); breathing acidosis is caused by insufficient carbon dioxide elimination. Agranulocytosis. marked by a sharp decrease in the number of circulating white blood cells, often caused by medicines or radiation. Anaphylaxis. an unusual or exaggerated allergic reaction, sometimes causing shock and death caused by foreign proteins or other substances. Anaemia. decreased number of red blood cells and/or haemoglobin. Malaria causes anemia through a rupture of red blood cells during merozoite release, as well as other mechanisms such as inhibiting red cell production in the bone marrow. anofelin. concerning Anopheles mosquitoes. prenatal care. the care and treatment of pregnant women and her unborn child. anthropophilic. attracts people, especially as a source of food (e.g. malaria-carrying mosquitoes). Antibody. proteins produced by the immune system in response to the introduction of a substance (antigen) recognized as foreign. The main purpose of antibodies is to interact with other components of the immune system and to make the antigen harmless. p. 335. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. molecule capable of detecting an immune response. antigen diversity. the ability of the body to alter its antigenic properties. antigen variations. as well as antigenic diversity. antipyretics. a means that reduces fever. Arthralgia. pain in one or more joints. aminotransferase. enzyme produced by the liver. If located at abnormally high levels in the blood, it may indicate inflammation or liver or other organ disease. Ataxia. and other inability to coordinate voluntary muscle movements. This finding indicates some nerve disorders, especially in the cerebellum. (as in the vaccine). to reduce the virulence of pathogenic agents. the auditors referred to the potential. electrical brain wave activity measured in response to acoustic stimulation (in sound mode). Evoced potential is used as diagnostic tools to investigate possible damage to the central nervous system caused by, for example, a disease such as multiple sclerosis or drug.brain stem. Part of the brain consists of a middle cat, pons, and spinal cord oblongata connecting the spinal cord with forebrain of the brain. bioassay. a method for determining the relative strength of the substance (as a drug) by comparing its effects on the test organism with that of the standard solution. Pack. the type of product packaging in which individual doses of one or more tablet types are administered in separate hermetic plastic pockets, often accompanied by dose instructions. Blister packs usually contain all the doses required for one treatment course.cardiotoxic. heart toxicity. cell-mediated immunity. an immune process in which subgroups of efficia T cells protect against viruses and intracellular protozoa infections such as malaria. Centrifuge. a machine that uses centrifugal force to separate substances of different densities, to remove moisture or to mimic gravitational effects. prevention of chemotherapy. medicines to prevent infection or progression of infection to disease. Chromosome. any of the normally linear intracellular structures containing the genes or hereditary factors of the eucalytic organism, bacteria or certain DNA viruses (e.g. bacteriophagics). cinchonism. with quinine or quinidine, reversible at lower doses or discontinuation of the medicinal product. Effects include ringing in the ears, Page 336 Share Cite Suggested Quote: Glossary. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. The term derives from cinchona bark, a natural source of quinine. clinical treatment. sometimes without all parasites. the co-formalisation of the combination of two or more medicines, i.e. two (or more) medicines per tablet. This differs from the combinations of drugs in separate tablets, either blister packaged together or from individual containers. Coma. consciousness from which the person cannot be aroused. Cost-effective. on the basis of the material benefits of the money spent. cost-effectiveness. value (efficiency) indicator of the resources spent (costs). Generally considered to be the ratio of the cost-effectiveness of a drug or procedure, for example, relates the cost of that drug or procedure to the health benefits resulting from it. In terms of health, this is often expressed as the annual cost of life saved or the cost of life saved. culicin. refers to mosquitoes of the genus Culex. other parasites. red blood cells containing mature malaria schizonts, which attach endothelium cells lining small blood vessels. cytokines. protein released by immune cells acting as an intercellular mediator in the process of developing an immune response. Examples of cytokine classes are interleukins and lymphomas. Cytotoxic. toxic to cells. Ddt. 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane or chlorphenotan, pesticide. degedege. Swahili term for febrile disease with seizures (often cerebral malaria), sometimes perceived as a nonmalarial condition with Causes. [test]. short term for rapid diagnostic testing (RDT), usually carried out by immersing a commercially prepared strip in body fluid. DNA. deoxyribonucleic acid, a genetic information medium (i.e. hereditary properties) found mainly in the cell nucleus. drug pressure. effects of certain medicinal products, usually an antimicrobial. dysdiadohokinnesi. the inability to stop one motor running and replace its opposite action, usually the result of a neurological disease. Page 337 Share Cite Suggested Quote: Glossary. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/1101 ×7 graphic tracking of electrical currents produced during contraction of the heart muscle. electrocardiography. a tool to record changes in electrical activity occurs during cardiac contraction, which is often used to diagnose abnormalities in cardiac conduction. Emax. the maximum effect of exposure to the medicinal product. In the case of antimalarial medicinal products, this usually reflects a reduction in the overall plastic burden after exposure to the product in question. Endemic. the presence of disease in the community. Holoendemic. have a significant impact on all residents of the area. hyperendemic. cause high but stable infection rate over time. hipoendemic. low but stable infection rate over time. endothelily cells. cells that jump into the heart cavities, blood and lymph blood vessels. entomological inoculation rate (EIR). measurements of the frequency with which an infectious mosquito is bitten by humans; or the average number of infectious bites received by a resident of the malarios region for more than one year or another period of time. Enzyme. any of the many complex proteins produced in living cells and to thymise specific biochemical reactions. Eosinophilia. abnormal increase in the number of eosinophils (a type of white blood cell) in the blood, allergic conditions and various parasite infections. Epidemic. a rapid and/or widespread outbreak of the disease through a community where the disease is not normally present or is at a low level. Epidemiology. disease and determinants in populations. Erythrocytes. red blood cell. Erythrocytes. red blood cells. erythrocyte stage. the life cycle of a malaria parasite that infects and develops inside red blood cells. exoerythrocytic stage. at the stage of the life cycle of the malaria parasite infects, develops, or remains latent in liver cells (hepatocytes). (or medicines). one of the groups of drugs that together includes safe, effective treatment for most of the infections and non-communicable diseases that currently affect the world's population. The 12th list of basic substances, drawn up by the WHO Expert Committee in 2002, contains 325 individual drugs. economic side effects: external impact means the costs (negative external impact) or the benefits (positive external ities) of an economic activity that affects someone who is not involved in an economic activity and which is not fully reflected in prices. As for malaria, when a large proportion of people in the community purchase and Page 338 Share Cite Suggested quote: Glossary. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/1101 ×7 doi: 10.17226/11017. malaria caused by plasmodium falciparum febrile species. fever. first-line therapy. treatment for a particular disease or condition.gamete. a mature male or female stem cell, which usually has a single set of chromosomes and is able to initiate the formation of a new diploid individual by entangling with a gamete of the opposite sex. gametocytocidal. can noned gametocytes. gametocyte. parasite that makes up red blood cells. Macrogametocytes (female) and microgametocytes (male) form individual erythrocytes, must swallow female mosquitoes, and combine mosquitoes in the stomach. gene amplification. process in response to certain cell developmental signals or environmental pressures leading to an increase in the number of copies of genes. In humans, this process is most often seen in malignant cells. genetically modified mosquito. mosquitoes with added or altered genes that either destroy developing malaria parasites or make mosquito-unsypt or fire-resistant host malaria. Genotype. the genetic composition of the organism or group of organisms other than the physical appearance; alle located on homologous chromosomes, which determine the specific characteristics or characteristics. 6-phosphate dehydrogenase (G6PD) deficiency. global enzyme deficiency in human erythrocyte, affecting around 400 million people worldwide. The deficiency confers some resistance to malaria, but also can lead to hemolytic anemia of various severiy, especially after exposure to certain drugs, including the antimalarial drug primaquine.half-life. the time required for half of the quantity of the substance (as a medicinal product or radioactive marker) to be disposed of or contaminated by natural processes in a physiological or ecological system. Hematocrit. ratio of the volume of wrapped red blood to the volume of unelsed blood determined by the centrifugation tool: measure of possible anaemia. heme dimerization. stage of biochemical distribution of human hemoglobin within the malaria parasite, which gives malaria pigment (hemozoin). Hemoglobin. protein in erythrocytes that carry oxygen. Page 339 Share Cite Suggested Quote: Glossary. in the field of medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/1101 ×7 condition in which the red blood cells rupture prematurely. Examples of hemolytic conditions are sickle cell anaemia and malaria. Hemolytic anemia occurs when the bone marrow is unable to compensate for premature destruction by increasing the production of new red cells. haemozoin. malaria pigment; decomposition product of hemoglobin containing iron, which accumulates as cytoplasm granules in malaria parasites and tissues of infected persons. hepatocyte. liver cell. hyperparasaemia. The number of parasites exceeds 250,000 per microlitre, or a country in which more than 5% of circulating red blood cells are parasitized. Hyperparasitemic patients have an increased risk of death from microvascular disease, as well as metabolic effects from high parasite loads. Hypoglycaemia. glucose is lower than the lower normal value (70-110 mg/dl [3.9-6.1 mmol/l as SI standard units]). Glucose levels 40 and below are severe hypoglycemia, a life-threatening accident. Hypoglycemia is common in malaria, as malaria parasitized red blood cells use glucose 75 times faster than uninfected cells. Treatment with quinine also lowers blood glucose levels by stimulating insulin secretion. Hyponatremia. serum sodium is lower than the normal lower limit of 135-147 mEq/l (135-147 mmol/l for SI standard units). Serum sodium levels approaching 120 and below are severe hyponatraemia, medical emergency. Hyponatraemia can be seen in malaria, and indicative of complex malaria. hypnotitis. stage of malaria parasites found in liver cells. After sporozoites invade liver cells, some develop into latent forms called hypnozoites. They become active months or years later, causing repeated malaria attacks. Only P. vivax and P. ovale produce hypnozotics in the human immune system. a natural protection mechanism in the body in which specialised cells and proteins in the blood and other elements of the body interact to prevent or neutralise infectious micro-organisms and other foreign substances. Immunity. the ability of the organism to control or influence a malaria attack with antibodies and other protective reactions that have developed in response to previous malaria attacks. Semi-immune individuals live in malaria endemic areas and are re-infected. Immunity reduces their symptoms and reduces the parasite. immunochromatography. an antibody-based process in which the components of the individual components use capillary flow through an absorbent membrane; used in research and is the basis for diagnostic tests. Page 340 Share Cite Suggested Quote: Glossary. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/1101 ×7 epidemiology, the number of new cases of the disease occurring during the disease is Period. Frequencies are the frequency with which new cases occur in the population over time. The denominator is the population at risk, and the counter is the number of new cases that occur over a certain period of time. the remaining indoor spraying (IRS). spraying long-lasting insecticides on indoor walls or rafters to kill resting insects, especially female malaria vectors, are based indoors after eating blood. integrated control. control involving more than one type of intervention. As for malaria, this could include a combination of drug treatments for symptomatic cases, prevention of ITNs, and environmental measures to reduce mosquito breeding. insecticide-treated bennett (ITN). a fine mesh net that is either treated with a long-lasting insecticide or produced with an insecticide directly incorporated in its fibers, hung over the bed to protect sleepers from insect bites. Insecticide-treated curtains (ITC) are located in windows and doors. intermittent prophylactic treatment (IPT). treatment of antimalarials during pregnancy to prevent clinical disease. This approach is now being extended to infants and can also be included in childhood immunization schedules in malaria endemic regions. current medicinal product. Erythrocytes. Intramuscular. in a muscle or is injected into a muscle. intrauterine growth restriction (IUGR). sex sing, usually defined as a child weighing less than 10 percentile of the expected weight of gestational age. Malaria may cause IUGR during pregnancy. intravascular. is located in a blood vessels. Intravenous. intravenous fluids for dehydration. Vitro. biological processes that take place in isolation from the whole organism, such as in a test tube or cell culture. in vivo. biological processes that occur in the living organism.jaundice. yellowish discolouration of the whites, skin and mucous membranes of the eyes caused by the deposition of bile salts in these tissues. This can be seen in various liver diseases, such as hepatitis, which affects bile treatment, as well as hemolysis (excessive destruction of red blood cells). It is also called icterus.knock down resistance (kdr). form of resistance to pyrethroid insecticides Page 341 Share Cite Suggested quote: Glossary. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 caused × by genetic point mutation. kdr is found in anofeline malaria vectors, as well as other mosquitoes and some other insects.larvicide. means of killing insect larvae (malaria, in the case of mosquito larvae). ligands. the place of attachment or molecule that binds to the extra site to another molecule. light microscope. laboratory microscope using conventional light (as opposed to parallel electrons, such as electrons under a microscope) to illuminate the object. Collapsing. disintegration or dissolution process (from cells).meningitis. the brain and spinal cord brain brain brain brain brain brain brain brain brain brain brain brain of brain inflammation, most commonly caused by bacterial or viral infection and characterized by fever, vomiting, intense headaches, and a stiff neck. merozoite. stage of malaria parasite, a human host that infects red blood cells. metabolic acidosis. resulting from excess acid due to abnormal metabolism (such as severe malaria), excessive acid intake, or renal retention or excessive loss of bicarbonate (as severe diarrhea). microhematoritis (tube). procedure to determine the ratio of erythrocyte volume to the volume of whole blood by centrifugation of a minute of blood in a capillary tube coated with heparin. Monotherapy. one medicine to treat the disease. molecular marker. genetic markers, usually proteins or DNA sequences, identified by biochemical methods. multigravidae. women who have had multiple previous pregnancies. Mutagenicity. the ability to cause DNA mutations. Myalgia. muscle pain. white blood cell counts, which mainly affect neutrophil counts. Cyst, located in the outer stomach wall of the female anopheline mosquito, where sporozoite development occurs. When mature, oocyst rupture and release sporozoites. Sporozoites then migrate to the salivary glands injected into the hosts when mosquitoes feed. ookinete. the form of a fertilized malaria parasite in the mosquito body. is rebramed. number of people than a competing population.parasitemia. parasites with or without clinical symptoms. Page 342 Share Cite Suggested Quote: Glossary. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/1101 ×7 sudden attack or increase in the intensity of symptoms, which usually occurs at intervals. Malaria is classically described as producing fever paroxysm-sudden severe temperature rise before chills and then abundant sweating. multi-annual transmission. (as opposed to seasonal) dispatch. peripartum. before, during or after delivery. pharmacodynamics. pharmacology sector dealing with reactions between drugs and living systems. Pharmacokinetics. interactions with humans that take them, as compounds are absorbed, metabolized, distributed and released. phenotype. the visible properties of the organism, obtained by interaction with the genotype (genetic composition) and the environment. a protozoa containing all malaria parasites affecting humans and other animals; any single malaria parasite. point mutation. gene mutations specifically related to the substitution, addition or deletion of genes monoucleotide bases. polymerase chain reaction (PSR). A method to increase the level of low specific DNA sequences, which makes it possible to determine very low antigen levels in the sample. Polymorphism. the existence of a gene in several allelic forms. during polypharmature therapy. prescribing of medicinal products. pre-media, was used for inocutially by a specific disease at a certain time. primigravidae. pregnant women for the first time. Prevention. measures designed to prevent diseases and maintain health: protective or preventive treatment. immunities. the presumptive treatment. use of antimalarials if suspected before laboratory tests are available to confirm the diagnosis. Prevalence. proportion of the population affected by a specific disease at a certain time. protozoe. single-celled animal. public goods. Things are either consumed by everyone in the community, or by noone at all. They have three characteristics. Public funds are: 1) non-censored- one person who consumes them does not stop the other person who consumes them; 2) nonexcludable—if one person can consume them, it is impossible to stop another person from consuming them; and 3) undeausable- people can not choose not to consume them, even if they want. Examples include clean air, the national defence system and the judiciary. The general public good cannot be provided by a single country acting alone, but only by the joint efforts of many (strictly, all) countries. Univer-Page 343 Share Cite Suggested Quote: Glossary. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. pulmonary tubes. abnormal accumulation of fluid in the lungs. pyrethrin. either two fatty liquid esters, $C_{21}H_{28}O_3$ and $C_{22}H_{28}O_5$, were extracted from dried chrysantheme flowers (the oldest effective insecticide) having insecticide properties and are the active ingredients of pyrethyroid. pyrethroids. any of the various synthetic compounds that are associated with pyrethrine and emulate them in insecticide properties.quartan malaria. malaria caused by Plasmodium malariae and characterized by recurrence bouts of chills and fever at 72 hour intervals.rapid diagnostic test (RDT). a quick, convenient and/or inexpensive method to determine whether a patient has a certain disease. Rbc. red blood cell count. Reagent. a substance used to identify, measure or synthesize a product due to its chemical or biological activity; Reactor. recombinant vaccine. a vaccine prepared by recombinant DNA technology in which the host organism (expression vector) is intended to produce specific molecules by segments of DNA from another organism (e.g. malaria parasite). In this way, vaccines that target specific antigens to parasites or parasites can be manufactured. recurrent malaria attack associated with the survival of malaria parasites in erythrocytes. Relapse. A repeated attack on malaria characterized by P. vivax and P. ovale, in which a repeat attack is repeated sowing in the bloodstream with latent hypnoticitis in the liver. reticular. related to the network or forming a network. reticused. immature erythrocyte cells that appear especially during the regeneration of lost blood and which are fine basophilic reticula are formed from the remnants of the ribosome. P. vivax only parasitizes recicyte. Chills. severe chill, characterized by shaking of the body.schizont. a multi-infant parasite that represents a mature stage of aborn malaria parasite. schizogony. aborn cycle sporozoa, especially life cycle malaria parasite red blood cells in humans. test or case definition property defined by a grade from Page 344 Share Cite suggested citation:Glossary. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. Specificity. the property of the test or case definition, determined by the degree to which it correctly identifies those who are not sick or in a situation of interest. splenomegaly. spleen. Often found in malaria patients, which can sometimes be detected by physical examination of the abdomen. sporoony. part of the sexual reproduction of malaria parasite, which occurs in the mosquito. sporozoite. stage of malaria parasites are injected into the bloodstream by biting infectious mosquitoes. Sporozoites infect liver cells, disappearing from the bloodstream within 30 minutes of entry. sterile insect technique (SIT). the mass release of sterile male insects to displace a normal male population, thereby reducing the number of females that are multiplying. Radiation is most commonly used to sterilize male insects, but genetic methods have also been developed. SIT has not yet played a role in malaria control, but research is taking place.tachycardia. heart rate of more than 100 beats per minute. tahipnea in both sides. increased breathing rate, more than 20 breathing times. Teratogenic. may cause structural abnormalities (i.e. birth defects) during fetal development. tertianalaria. malaria caused by Plasmodium vivax or Plasmodium ovale, characterised by chills and fever 48 hours apart. Thrombocytopenia. platelet count, defined as less than 150,000 per ml. Low platelet counts may interfere with blood clotting and increase the risk of spontaneous bleeding below 50,000/ml. multi-tiered pricing. a mechanism for the segmentation of the world market used in the case of medicinal products to make poor countries pay lower prices than the richest; also called fair or different prices. trophozoite. aborn grows up malaria parasite in human blood cells, causing a mature schizont.vector. an agent that carries the disease from one host to another, such as a mosquito that transmits a malaria parasite. vivax malaria. malaria caused by malaria parasite Plasmodium vivax.wild type [genes]. a phenotype, genotype or gene that dominates the natural organism population or body strain, as opposed to natural or laboratory mutant forms; organism or strain that pulled out the wild type. p. 345. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 × zoophagic. preferring lower animals to humans as a source of food. zoo prophylaxis. the diversion of diseases from humans to animals transported from humans. Page 346 Share Cite Suggested Quote: Glossary. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. Page 334 Share Cite Suggested Quote: Glossary. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017. × page 335 Share cite suggested quote:Glossary. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × Page 336 Share Cite Recommended Quote: Glossary. 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As described, MMSS would be responsive to qualifications in national malaria control programs, NGOs, and other private sector organizations. MMSS is proposed as a time-limited target that will be phased out when endemic countries develop their ability to assume procurement (and other) responsibilities. The MMSS currently described in the draft document would be in line with some of the objectives of the report's recommendations and could evolve to suit all. One obvious difference is that MMSS is described as a time-limited organization. It is unclear whether the need for this function will diminish in the near future. If it works well, it could be a permanent, effective mechanism for antimalarial procurement. Another important issue that remains to be addressed is the mechanism for global ACT subsidy injections into the system in a way that will affect the private retail sector. 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Khoromana CH, Campbell CC, Wirima JJ, Heymann DL. Efficacy of chloroquine therapy in vivo Plasmodium falciparum malum in children below the age of five years. American Journal of Tropical Medicine and Hygiene 35 (3):465-471. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017. × 8 Malaria control This chapter reviews malaria control over the last century, tracking malaria to depart from much of the world in its current line of demarcation. It also describes individual control methods that focus on both mosquito vectors, human reservoir infections, as well as the current state of diagnosis and vaccine development. The chapter concludes that malaria control strategies are under discussion, including national and regional policies and programmes that are in place today. Historically, malaria reaches far beyond the tropics. Until the 19th century, transmission took place in large parts of the temperate world, including England, Holland, Germany, Central and South-Eastern Europe, Asia, India, China and america (Schiff, 2002). In North America the disease reached as far north as New York, and even Montreal (Barber, 1929). In the early 20th century, the Tennessee Valley Authority built hydropower plants in the southeastern United States, modernizing the region. As housing and lifestyle improved, and human reservoir infections declined, malaria receded (Desowitz, 1999). In the first half of the 20th century, malaria disappeared from the largest of Europe, following land-use change, farming practices, house building and targeted vector control (Greenwood and Mutabingwa, 2002). p. 198. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × came the golden days of DDT, a highly effective insecticide first used as a delousing agent at the end of World War II. In the 1950s and 1960s, the remaining spraying of indoor sittings with DDT was at the heart of the world's malaria eradication efforts. DDT was able to kill or deter adult women for months resting on treated walls after feeding led to further declines in malaria in India, Sri Lanka, the former Soviet Union and other countries. By 1966, more than 500 million people (about one third of the population previously living in malarios) had been freed from the threat of disease by campaigns using DDT spraying, eliminating mosquito breeding sites and mass treatment (Shiff, 2002). Unfortunately, eradication was not sustained due to the high program costs, community resistance to repeated home spraying, and the emergence of resistance to DDT. By the end of the 1960s, the hope of eradicating malaria through vector control was finally abandoned (Guerin et al., 2002). In many countries, the pendulum then swung to an overreliance of chloroquine, a widely available antimalarial drug. Sub-Saharan Africa was always a special case. With the exception of some pilot programs, no sustained malaria control efforts were ever installed there (Greenwood and Mutabingwa, 2002). The biggest obstacle was the widespread Anopheles gambiae, long-lived and aggressive malaria vector spread. The rate of entomological inoculation (EIR) (which determines how often a human bites an infectious mosquito) in Asia or South America rarely exceeds five years. By contrast, more than 1000 EIR are registered in more than 1000 parts of Africa (Greenwood and Mutabingwa, 2002). Today, the global burden of malaria is concentrated in sub-Saharan Africa, where stable endemic diseases are linked to poverty and very effective vectors. Insecticide-treated bednets (ITN)-first seen in Gambia to reduce total child mortality by 60 percent when combined with malaria chemoprophylaxis (Alonso et al., 1991)-is a vector control tool with the greatest promise to Africa. At the Africa Summit on Roll Back malaria in Abuja, Nigeria in 2000, leaders from 44 African countries set a target of 60 percent ITN coverage for pregnant women and infants in Africa by 2005, an ambitious target requiring about 160 million ITNs with an estimated cost of $1.12 billion (Nahlen et al., 2003). Unfortunately, the target has not yet been achieved. At the same time, insecticides resistance (which includes pyrethroids and DDT) is a growing problem in Africa, as well as environmental changes brought about by agriculture and other forms of development that promote mosquito breeding. International sponsors have also withdrawn their support for DDT for environmental reasons. As regards the human reservoir of malaria, the main challenge for Africa is the development of plaque falciparity resistance to drugs (chloroquine and sulfaxine- 199: Part Cite Recommended Citation:8 Malaria control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 × (SP)), complicated by large and in some cases a moving infected population. malaria control programmes have traditionally been used for a number of interventions. In 1952, Paul Russell (noted by the Rockefeller Foundation's Malaria and former Head of the Allied Anti-Malaria Campaign in Italy) lists five approaches to the eradication of malaria (Russell, 1952): Measures to prevent mosquitoes from feeding mosquitoes (human vector contact) Measures to prevent or reduce mosquito breeding Measures to kill mosquito larvae, to destroy or reduce the life span of adult mosquitoes Measures to prevent malaria parasites from humans since the Russell era, more emphasis on human disease control has led to three additional strategies (Beales and Gilles, 2002): Measures to prevent and reduce malaria mortality (especially in high-risk groups) Measures to reduce the incidence of malaria Measures to reduce malaria transmission Today's control efforts are mainly based on stopping and reducing the exposure of human vectors and treating infected individuals. Personal protection through ITN or curtains usually prefer settings where vectors feed indoors during nighttime sleep hours. Itn also kills malaria vectors and reduces local transmission intensity (mass effect). Indoor residual spraying (IRS) with DDT or pyrethroid insecticides is another way to reduce bites with vectors whose feeding and resting habits make them susceptible while most homes in the target community are sprayed. The IRS is also the preferred vector control method during malaria epidemics and in refugee camps, as trained spraying units can quickly cover possible transmission areas. Case management, which includes quick access to healthcare, accurate diagnosis and effective treatment, is the second cornerstone of malaria control. The current inability to control malaria with drugs often begins with the inability to ensure proper case management for many malaria sufferers, especially in the periphery of the health system. Other control strategies presented by the World Health Organisation (WHO) in 1993 include early prediction of malaria epidemics and the cite proposed cite on page 200: 8 control of malaria. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi:

10.17226/11017 doi: 10.17226/11017 ×. capacity building in the field of basic and applied research; and the assessment of ecological, social and economic factors for diseases (WHO, 1993). Efficient field operations also require knowledge and teamwork. Qualified staff with knowledge, skills and authority are perhaps one of the most important resources needed for effective vector control (Roberts et al., 2000). The same need for knowledge applies to those who make clinical care for malaria patients: from parents, village health workers, drug and traditional healers to laboratory staff, staff, doctors and other healthcare professionals. Immediately after the Second World War, DDT and other chlorinated hydrocarbon insecticides formed the main pillar of malaria control. DDT was originally developed as a public health insecticide before its widespread use of agriculture and its recognition as an environmental pollutant (Curtis and Lines, 2000). To be taken into account when used indoors in limited quantities, the entry of DDT into the world food chain is minimal (Attaran et al., 2000). (For a full summary of the role of DDT in public health, readers are referred to in a recent review [Taverne, 1999]). Today, despite concerns about their environmental impact and the possible inactivation of mosquito carriers, chemical insecticides remain key elements in the control of malaria. A WHO-coordinated research programme has now been put in place to develop insecticides for new candidates and to test their performance and safety (WHO, 1996a). The specifications for pesticides used for public health are part of the WHO Pesticide Assessment System (WHOPES). Classified according to chemical properties, the most common insecticides, currently used in public health practices are: petroleum oils and their derivatives Chlorinated hydrocarbons (e.g. dichlorodiphenyl trichloroethane (DDT), hexachlorocyclohexane (HCH) and dieldrin) components of the active pyrerum flower (pyrethrin) or of this group of synthetic compounds (pyrethides) (e.g. dichlorodiphenyl trichloroethane (DDT), hexachlorocyclohexane (HCH) and dieldrin) Phosphorganic insecticides (e.g. malathion and temefoss) Carbamates (e.g. propoxur and carbaryl) Insect growth regulators (e.g. diflubenzuron, metokene and pyriproxyfen) Page 201 Share Cite Preferred quote:8 Malaria control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. ×, an extract of dried chrysantheme flowers, is the oldest effective insecticide known. Both pyretra and its natural and synthetic relatives (pyrethramines and pyrethroids) are nerve poisons that spread rapidly and kill adult insects with a high limit of mammalian safety. They also demonstrate quick knock-down (i.e. immobilization) and repellent effects. The main drawback of the class is relatively short-term activity, although newer synthetic compounds such as permethrin and deltamethrin are more stable than naturally occurring products. In turn, DDT residues are active for up to a year on impermeable surfaces such as plastered walls (on mud bricks, DDT loses its insecticide exposure faster). The long-term repellent and contact-irritating effects of DDT probably contribute as much or more to its direct insecticide action by controlling malaria transmission (Robert et al., 2000). At the molecular level, all major chemical insecticide classes produce the main effects of target insects in nerve tissues. DDT and pyrethroids cause continuous sodium channel activation (Soderlund and Bloomquist, 1989), while pyrethroids also receptors that normally regulate inhibitory neurotransmission and organophosphates and carbamates have acetylcholinesterasis. The level of resistance in insect populations reflects the amount and frequency of insecticide contact and the characteristics of the target species. So far DDT resistance has not developed in long-lived disease carriers such as tsetse flies or triatomy bugs (the final hosts of African sleep disease and Chagas disease, respectively). Mosquitoes, in turn, have several characteristics suitable for rapid development of resistance, including a short life cycle and abundant offspring. In 1946, only two species of malaria vectors were resistant to DDT. However, until 1966, the emergence of resistance was clear: 15 species were resistant to DDT and 36 species were resistant to diedrin (WHO Committee of Insecticide Experts, 1970). By 1991, 55 anotin vectors showed resistance to one or more insecticides. Of these, 53 were resistant to DDT, 27 to organophosphates, 17 to carbamates and 10 to pyrethroids (WHO, 1992a, b). Ten years later, a known type of pyrethroid resistance resistance (either reduced mortality or reduced cases of mosquito excito reeject with pyrethroid impregnated ITN) was reported from Asian, African and South American countries (Takken, 2002). The three main groups of inactivating enzymes (gluton S-transferase, esterases and monooxygenases) are responsible for metabolic resistance to DDT, pyrethroids, organophosphates and carbamates in the afeel mos-Page 202 Share Cite Recommended hardening:8 Control of malaria. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/1101 ×7 Knock-down resistance (kdr) is a separate resistance phenotype associated with a sodium channel point mutation aimed at both pyrethroids and DDT. Although it is common in A. gambiae in West Africa, the DRC has not reduced the effectiveness of ITNs in the region (Sina and Aultman, 2001; Hemingway and Bates, 2003). South African, by contrast, local vector A. funestus has gained metabolic resistance to pyrethroids, making ITNs ineffective (Chandre et al., 1999; Brooke et al., 2001). The looming concern for the future is that A. gambiae in equatorial Africa will gain the same metabolic resistance to pyrethroids seen in A. funestus in South Africa. Currently, metabolic resistance to pyrethroids A. gambiae is limited to key areas in West Africa and Kenya (Ranson et al., 2002). In the coming years, strategies to reduce insecticides resistance may include rotation of agricultural and environmental insecticides, mosaics and mixtures led by mathematical models (Tabashnik, 1989). To date, some on-the-spot testing of models has been carried out; however, new biochemical and molecular field instruments shall have a wide-ranging resistance management test possible. Treating ITNs with two insecticides with another approach that can be taken in the near future. In West Africa, two-treated networks pairing pyrethroids with carbosulfan (carbamate insecticide) or chlorpyrifos-methyl (organophosphate insecticide) (Muller et al., 2002) are currently being evaluated. More than two thousand years before Ronald Ross and Giovanni Battista Grassi showed that mosquitoes transmit malaria, people use nets to fend off night-biting insects. Mosquito nets appear in historical records from the Middle East to West Africa to Papua New England (Lindsay and Gibson, 1988). Greek writer Herdūti (484 - ?425 BC) describes how Egyptians living in swampy lowlands protect themselves with fishing nets. Every man there has a net that he uses for day fishing, but at night he finds another to use it: he drapes it over the bed... and then crawls under and goes to bed. Mosquitoes can bite with any cover or linen blanket... but they don't even try to bite through the net. Herdotuss, History History Page 203 Share Cite Recommended Quote:8 Malaria Control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017. × at the beginning of the 19th century, British colonists in India, most likely inspired by the punjabi fishermen's example, also slept under the nets. However, it was only during the Second World War that textiles and insecticides were combined. In Central Asia, the Soviet army applied cadital oil to bednets to ward off mosquitoes, and sand flies bearing malaria and leishmania (Blagoveschensky et al., 1945), while the American military pacific theater impregnated bednets and jungle hammocks with 5 percent DDT to ward off malaria and filariasis (Harper et al., 1947). Interest in insecticide-impregnated networks as a malaria control tool resurfaced in the late 1970s and early 80s. Until then, synthetic pyrethroids were the logical choice of insecticide because of their low mammalian toxicity and some efficacy in killing and repelling various disorders and disease-bearing insects. Several governments, including the Philippines, Solomon Islands and Vanuatu, began to include the promotion of ITN as one of their malaria control objectives (Chavasse et al., 1999). However, the most successful government-funded ITN programs today are found in China and Vietnam, where the public sector's main investment is to offer regular net re-treatment services. If repeated treatment is provided free of charge (e.g. In China and Vietnam), coverage is usually high (Curtis et al., 1992). Conversely, in Africa, where many networks and insecticides are provided free of charge or at subsidised prices through local projects and NGOs, less than 5 to 20 per cent of the networks are re-processed (Snow et al., 1999; Rowley et al., 1999. Guillet et al., 2001). After several small-scale studies in the 1980s, the first large-scale study on ITN plus 60 per cent reduction in all-cause child mortality (Alonso et al., 1991). These results prompted the UN Development Programme/World Bank/WHO Special Programme for Tropical Disease Research and Training (PDR) to sponsor four randomised controlled trials in Africa to assess the impact of ITNs on all-cause mortality in African children under different epidemiological conditions. The cluster randomization design was used in all four studies. In the Gambia (D'Alessandro et al., 1995), a 25 percent decrease in all-cause mortality was observed in children under the age of 9 years. In Kenya (Nevill et al., 1996) and Ghana (Binka et al., 1996), the introduction of itn was associated with a 33 and 17 per cent reduction in all-cause child mortality in children under 5 years of age, respectively. Study populations in all three sites ranged from 60,000 to 120,000 (Table 8-1). The fourth randomised controlled trial in Burkina Faso (Habluetzel et Page 204 Share Cite Suggested Quote:8 Malaria Control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × Table 8-1 ITN protection effectiveness: reduction in child mortality in five randomised controlled trials National of a percentage reduction in child mortality in EIR Gambia (D'Alessandro et al., 1995) a 25% 1-10 Kenya (Nevill et al., 1996) 33% 10-30 Ghana (Binka et al., 1996) 17% 100-300 Burkina Faso (Habluetzel et al., 1997) 15% 300-500 Kenya (Phillips-Howard et al., 2003) 16% 200-300 aThis study was considered to be effective, as opposed to efficacy, in the study. al., 1997) tested insecticide-treated curtains (ITC) instead of beds in about 100,000 people in the region with variable seasonal high and low malaria. The initial mortality rate, which approached 45 per thousand, was by far the highest of the four African ITN studies (Diallo et al., 1999). After 2 years of tracking, ITC use was associated with a 15 percent reduction in all-cause mortality in Burkina Faso, concentrated in the first year of use. Considered a group, four PNR-sponsored randomized controlled trials have shown reducing ITN efficiency with increasing transmission pressures because sites experiencing higher EIRs (100-500 infectious bites per person per year, i.e. Ghana, and Burkina Faso) experienced lower ITN benefits. The last group randomised controlled study of permethrin-treated bednets conducted in western Kenya (Hawley et al., 2003a) was developed to evaluate the efficacy of ITNs in the upper transmission range throughout the year. This study gave an overall protective effect in 16 percent of all-cause child mortality; thus, the benefits of ITN were confirmed in a very high transmission area. However, the maximum exposure was dependent on regular itn re-treatment. For example, the protective efficacy of ITN in children aged 1 to 11 months from 26 to 17 percent when retreatment was delayed after 6 months. Commission 201 201 studies also showed a reduction in approximately 90% transmission compared to the initial EIR of 60-300 (Gimnig et al., 2003b). When ITNs are combined with highly effective therapies such as artemisinin combination therapy (ACTs) – even in highly endemic areas, it's possible that the EIR could drop even further, approaching 0 (Personal communication, N. White, Mahidol University, February, 2004). Page 205 Share Cite Suggested Quote: 8 Malaria Control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. Data from a large meta-analysis suggest that the use of ITN under stable transmission conditions is approximately half a year from mild malaria episodes in children under five years of age (Lengeler, 2001). In a nonrandomized study of ITNs in southwestern Tanzania, treated networks assigned protection efficiency of 62 and 63 percent, respectively, for parasitemia and anemia in children under 5 (Abdulla et al., 2001). In an area with high perennial transmission in Western Kenya, ITNs delayed the time of the first infection in infants from 4.5 to 10.7 months (ter Kuile et al., 2003a). Recurrent malaria infection also causes anemia and morbidity in pregnant and newborns. Four randomized controlled studies of ITNs during pregnancy have shown variable benefits in different transmission settings. In Thailand and the Gambia (areas with lower seasonal transmission), ITN significantly reduced malaria parasitemia and maternal anaemia (Dolan et al., 1993; D'Alessandro et al., 1996); In the Gambia, they also increased birth weight (D'Alessandro et al., 1996). However, no similar benefits were observed in areas with more intensive transmission (Coastal Kenya and Ghana) (Shulman et al., 1998; Browne et al., 2001), which raises concerns that ITNs could not protect pregnant women in areas with very high EIR. These concerns were raised by the latest findings. In a western Kenya study, full data on nearly 3,000 pregnancies were available (ter Kuile et al., 2003b). Before the start of the study, up to one-third of all infants were born prematurely, of a low gestational age or with a low birth weight. ITN-taking pregnant women (gravidae 1-4) experienced a 38 percent reduction in maternal parasitemia, a 47 percent reduction in malaria anemia, and a 35 percent reduction in placental malaria at the time of delivery, while their newborns showed a 28 percent reduction in low birth weight. In addition to granting benefits to individual users, ITN can protect non-users in ITN households as well as in nearby homes. Such effects were first observed in early village-scale ITN studies in Burkina Faso (Robert and Carnevale, 1991), Tanzania (Magesa et al., 1991), Kenya (Beach et al., 1993) and Zaire (Karch et al., 1993). Recent ITN studies have confirmed vector populations (Hii et al., 1997; Binka et al., 1998. Hii et al., 2000; Howard et al., 2000; Maxwell et al., 2002). Some data from the ITN study have even shown spatial effects on health. In Ghana, child mortality increased by 6.7 percent for every 100 m from intervention compound (Binka et al., 1998), Page 206 Share Cite Suggested Citation:8 Malaria control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. The minimum ITN coverage required to achieve community benefits is 50 to 60 percent of households in the neighborhood with suitable indoor, night-biting vectors (Hawley et al., 2003b). In Asia, in turn, ITNs have had mixed results because vectors often bite out late at night (or sometimes early in the morning), and both children and adults are susceptible. Currently, one insecticide treatment of conventional cotton or nylon mosquito nets lasts 6 to 12 months. Long-term insecticides (with insecticide included directly in net fibers) eliminate the need for regular re-treatment. Two prototypes (Olyset and Permanet) are now on the market, while others are being developed (Moerman et al., 2003). One of the early problems with Permanet produced by Vestergaard was the inconsistency between the parties; In a study randomly sampled from young, unwashed, traditionally washed, and up to 18 months of field-based insecticides, insecticides were significantly reduced after two weeks of washing, and mosquito mortality reached unacceptably low levels after just 12 months (Muller et al., 2002). These problems may have been resolved because Vestergaard-produced Permanets has now been approved by the WHO, and production is slated to increase to one million networks per month (Personal Communication, B. Greenwood, London School of Hygiene and Tropical Medicine, March 2004). Sprayed insecticides to kill adult mosquitoes were introduced on a large scale in the mid-1930s. Pyrethrum was first used for indoor residual spraying (IRS) in South Africa and India and later replaced by DDT after World War II. The IRS is most effective in reducing mosquitoes that rest indoors after eating blood. To be effective, the IRS doesn't kill all anopheles at once, but simply prevent a large portion of surviving 12 to 14 days (the time it takes for the malaria parasite to develop into an infectious phase of the mosquito). Even with solid vectors, this can be achieved with daily mortality of between 40 and 50 percent. In places with lower malaria endemicity, daily mosquito mortality of between 20 and 25 percent is generally adequate (Beales and Gilles, 2002). Just as ITNs extend the benefits of nonusers to society, the IRS is particularly effective when applied to a large because it increases the life span and overall transmission of the mosquitoes. This so-called Page 207 Share Cite Recommended Quote: 8 Malaria Control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. Specific examples are three demonstration projects in Africa: an observational study in the Pare-Taveta Malaria Scheme in Tanzania, where dieldine reduced the transmission of malaria from 10 to <1 (Pringle, 1969; Bradley, 1991); a study in Kisumu, Kenya, where the IRS with fenitrothion reduced malaria transmission by 96 percent from baseline in 2 years (Payne et al., 1976); and the Garki project in northern Nigeria, where the IRS with propoxur also significantly reduced transmission and improved infant and child mortality (Molineaux, 1985) (Box 8-1). Over the past 30 years, the DDT-based IRS has declined, in part, due to DDT resistance among malaria vectors. The continued lack of government support and funding, as well as the general rejection of DDT by the international community, have also contributed to the limited use of the IRS in sub-Saharan Africa. In parts of Asia, Latin America, as well as southern and northeastern Africa, where the IRS is still used, it is usually organized and paid by governments (for example, government-funded DDT house spraying was recently restored in KwaZulu Natal, South Africa, and Madagascar's highlands due to the increasing prevalence of pyrethroid-resistant A. funestus vectors and human malaria cases [Hargreaves et al., 2000]). The IRS also uses urban epidemics and refugee camps around the world, and is sometimes provided by foreign and multinational companies to protect workers and local communities in endemic areas of malaria (Sharp et al., 2002a). The introduction of the IRS is not trivial, and if incorrectly carried out, can be quite ineffective (Shiff, 2002). Homes and animal shelters in the target area must be received by the IRS before the transmission season begins and thereafter at regular intervals. Before using the insecticide, all furniture, hanging clothes, kitchen utensils, food and other items must be removed from human settlements and left outside. Insecticide emulsions or solutions are often preferred, allowing the dilution of suspensions of water dispersible powders that leave a whitish precipitate. Mud and porous gypsum walls retain less IRS insecticide than wood or non-absorbing surfaces. Both itns and INs require user collaboration, albeit in different ways. In order to maintain expanded efficiency, the current generation of ITNs should be properly installed, reliably used and insecticide every 6 to 12 months. The IRS, by comparison, is passive but intrusive. Some residents of endemic areas lose the IRS benefits by painting or replastering sprayed walls, while other families avoid the IRS altogether with in the spraying round of their home (Mnzava et al., 2001; Goodman et al., 2001). In addition, some housing or shelter materials such as plastic films are not appealable to the remaining sprays. Page 208 Share Cite Suggested Quote: 8 Malaria Control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. The experiment was carried out in a group of villages near the town of Garki in northern Nigeria. The villages were divided into three intervention groups. Villages in the A1 group received household spraying with propoxor and mass drug use (MDA) with sulphase-pyrimethamine every 2 weeks, as well as limited larvae control with temephos (Abate). Villages in group A2 received household spraying with propoxsurus plus MDA with sulphalene-pyrimethamine every ten weeks. Villages in Group B received only household spray with propoxur. Group C villages served as controls. The main results of the Garki project were as follows: Household spraying with propoxur was relatively ineffective in reducing the indigenous population of anopheles gambiae, possibly due to outdoor recreational behaviour, and/or high sporzoite levels. In villages where the remaining spray was combined with MDA, especially in the group A1, where MDA was given every two weeks throughout the transmission season, there was a significant drop in Plasmodium falciparum parasitemia below 1 percent. The number of deaths decreased in both control and intervention areas, although some evidence showed a more pronounced impact in intervention villages. After the cessation of intervention, the parasite increased interference compared to control villages. However, there was no increase and post-nitration monitoring after intervention did not reveal rebounds in clinical cases or deaths. The Garki project was planned at a time when the eradication of malaria was still considered a serious opportunity for very endemic areas such as Nigeria. The experiment showed that transmission interruption was not possible even when malaria control instruments were used full of armania. Its findings helped shift the focus from eradication to the control of the clinical effect of malaria in Africa. Although the study did not focus on malaria-related morbidity and mortality to the same extent as it might be today, its parasitic data suggest that mortality and morbidity from malaria would have drastically decreased in study villages within 2 years of integrated malaria control. Brian Greenwood, London School of Hygiene and Tropical Medicine Page 209 Share Cite Recommended Quote: 8 Malaria Control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: The National Press. doi: 10.17226/11017. × Despite the proven advantages, the current use of ITNs in sub-Saharan Africa is also low. Most households in malaria endemic areas are not net, insecticide is treated or not. In nine African countries surveyed between 1997 and 2001, on average 13 % of households had one or more networks of any kind; on average, 1.3 per cent of households in three countries that own at least one ITN; and in 28 countries only 15 percent of children under the age of 5 slept under any network (WHO/UNICEF, 2003). Not surprisingly, net ownership and use are lowest in poor households. In addition to the cost of purchasing and re-treatment, another additional obstacle to ITN use is the common misconception that ITNs are designed to control mosquitoes rather than malaria. In cities with raw sewage and high-year population disturbance culicine mosquitoes, this misuse favors ITN use. However, in rural areas, the density of mosquitoes and mosquito disturbances are generally lower, despite the year-round fixing of secret female anefelines. As a result, ITN use is rarely prolonged night after night, especially during the dry season (Gyapong et al., 1996; Binka et al., 1996. Binka and Adongo, 1997). In western Kenya, itn use was observed in almost 800 households (Alaii et al., 2003a). About 30 percent of ITNs in homes were not used. Children under 5 years of age were less likely to take ITNs than the elderly, and ITNs were more commonly used in colder weather. Neither the number of mosquitoes, the relative wealth, the number of home dwellers, nor the level of education of the head of the household affected adherence. Excessive heat was often cited as a reason not to use a child's ITN. The researchers also commented on the efforts required by caregivers to store and rearrange ITNs every day (Alaii et al., 2003a). Finally, misunderstandings about malaria include lower incentives to use ITN and/or the IRS. In southern Ghana, the Adangbe people believe that Asra, a local disease that resembles malaria, is the result of prolonged exposure to heat (Agyepong, 1992). In the Bagamoy area of Tanzania degedege – local fever and seizures – is often blamed for bird spirit rather than brain malaria (Makemba et al., 1996). In western Kenya, many participants in the ITN study considered malaria to be a multi-bone disease and that therefore ITN was only partially effective (Alaii et al., 2003b). In areas with high malaria transmission, the prevalence of infection may vary considerably over relatively short distances. This has been observed not only in Africa (Greenwood, 1999), but in other countries such as Papua New Page 210 Share Cite Recommended Quote: 8 Malaria Control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × (Graves et al., 1988) and Pakistan (Strickland et al., 1987). Local factors insecticide impregnated materials) that affect the microeidemiology of malaria include the location, screening and construction of the house, the proximity of animals to human housing and the use of mosquito deterrents such as repellents, aerosols and fumigants. Despite the fact that anopheline mosquitoes can fly for significant distances, the proximity of houses or villages to the growing place strongly affects the risk of malaria, especially when breeding sites are limited. In the dakar suburb of Senegal, the prevalence of malaria grew rapidly from the center to the edge of the city, which is adjacent to the swampy breeding sites of Anpheles arabiensis (Trape et al., 1992). In Sri Lanka, the risk of malaria was much higher among those living in poor-quality homes 2.5 km from the river where A. culicifacies grew (Gunawardena et al., 1998). The design and construction of the house also affects the risk of malaria (Schofield and White, 1984). Eaves that allow interior ventilation, and smoke from cooking fires escape, are a common feature that facilitates mosquito access to sleeping areas in the home tropics. Using mud or plaster to fill the cornice (Lindsay and Snow, 1988), or hanging cornice curtains (Curtis et al., 1992) reduce human vector contact. In Sri Lanka Gunawardena et al. (1998) estimates that the costs associated with improving all low-quality housing (which the population suffered from a four-fold risk of malaria compared to families living in well-designed homes in the same area) would be balanced against savings in the cost of malaria treatment over 7 years. In some communities, animals live in or near homes. Zooprecrement is a term that suggests the possible diversion of the mosquito bite from humans to nearby animals. However, this diversion is entirely dependent on local vector bites and varies from species to species. In some cases, livestock may actually attract certain mosquitoes that would otherwise avoid human habitat, resulting in an increase in the exposure of household members to malaria (Hewitt et al., 1994; Bouma and Rowland, 1995; Mouchet, 1998). In Pakistan and in Afghan refugee camps, malaria cases were concentrated in communities where cattle were kept, possibly because local vectors A. culicifacies and Stephensi mainly attracted these households (Bouma and Rowland, 1995). p. 211. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × communities use aromatic smoke to deter mosquitoes. In Gambia, tree bark combined with synthetic scents (locally known as churai) reduced the number of mosquitoes entering the room, but not the incidence of malaria (Snow et al., 1987). By contrast, traditional fimigantes in Sri Lanka reduced malaria (van der Hoek et al., 1998). In Thailand, the deet mixture (N,N-diethyl-m toluamide) and paste made of local wood (wooden apple) was effective (Lindsay et al., 1998). Commercially produced coils containing pyrethroids or DDT are also reejected by mosquitoes (Charlwood and Jolley, 1984; Bockarie et al., 1994). Although reels are cheap, households can spend significant amounts of money on these types of items. In Dar es Salaam, Tanzania, the average household expenditure on antimosquito measures was USD 2-3 per month (Chavasse et al., 1999). Since A. gambiae can breed in virtually any puddle, larval control in sub-Saharan Africa has always been difficult. Where the number of breeding sites for vectors is low and easily identifiable, environmental or biological control of larval breeding sites is often possible. Oil larvicides have played an important role in mosquito control since the beginning of the 20th century. Production sites may also be eliminated by draining or filling basins, changing the boundaries of river or sewage systems and creating accumulation (reservoirs behind dams). The occasional drying of rice fields, brook locks or risings, salinity of coastal swamps or lagoons (e.g. using tides), the shading of stream banks and the cleaning of vegetation are naturalistic manipulations that proved to be beneficial for the control of some vectors, mainly in India and South-East Asia. Although overshadowed by the remaining insecticide for decades, many of these environmental methods of vector control are now back in vogue with strong WHO approval. Biological control strategies, including bacteria such as Bacillus thuringiensis subsp. sepedo, have been developed in the case of bacteria. Karch et al., 1993; WHO, 1999; Kaneko et al., 2000). Bti spores produce toxins that are poisonous to mosquitoes and other aquatic insects, but harmless to plants, animals and humans. Bacillus sphaericus (Bsph) is multiplied in contaminated waters and produces longer-acting toxins than Bti; However, resistance to BSF toxins is present in some mosquito populations in India, Brazil and France (WHO, 1999). p. 212. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. The oldest form of genetic control is sterile insect technology (SIT), a proven strategy in previous campaigns against boltworms, tsetse flies and Mediterranean fruitflies. Unfortunately, when mass hybrid sterility was tried against A. gambiae in Burkina Faso, West Africa, some mating actually occurred between sterile male and wild female anophelines. The production of a large number of sterile but competitive male mosquitoes and their successful release into the wild are still Obstacles. First predicted decades ago by Curtis (Curtis, 1968), genetically modified mosquitoes are now another potential means of vector control. The justification is as follows: Since only a few anopheline mosquitoes transmit malaria, genes that encode a non-transmission phenotype, or genes that prevent the disease of malaria parasites in general, can be inserted into the vector genome (Collins, 1994; James et al., 1999). The likelihood of this approach was recently demonstrated when a synthetic gene inserted into A. stephensi almost completely prevented its ability to transmit strains of rodent malaria (Ito et al., 2002). However, the same practical obstacle to THE BTI, namely the rapid replacement of local mosquito populations, affects genetically modified mosquitoes. Concerns were also raised about the suitability of genetically modified mosquitoes, the negative consequences of unstable genetic modifications and public objections to the placement of genetically modified organisms (Clarke, 2002). The main goal of malaria treatment is to save lives. Rapid, effective treatment in the early stages of falciparum malaria reduces the risk of death by up to 50 times, but effective treatment after progression to severe disease leads to only a five-fold reduction in the risk of death (White, 1999). However, malaria treatment can also reduce the transmission of malaria in endemic areas. This section assesses the role of treatment as a control measure that is capable of reducing the transmission of malaria, as well as past and current chemotherapy strategies for the population of malaria endemic areas. (For details on antimalarial medicines, drug resistance and treatment protocols, see Chapter 9.) The main objective of many early studies on wide spread against the edges was to stop the transmission of malaria (Greenwood, 2004). Two approaches were tried: treatment of symptomatic cases; and mass drug Page 213 Share Cite Suggested quote: 8 malaria control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. This finding that the treatment of symptomatic individuals could indirectly protect the entire malaria population, dating back to Robert Koch and the early 20th century (Harrison, 1978). At the time, partly in mind this objective, the use of quinine was widely used in Italy and elsewhere. Since quinine has little effect on gametocytes, however, it had little effect on transmission as a whole. Today, in turn, artemisinin-based drugs (which kill early-stage gametocytes as well as averse parasites) have helped reduce transmission in selected areas of Asia and Africa. On the border between Thailand and Burma, where field studies using the AKT were first carried out in 1991, meflline-artesuate as first-line symptomatic malaria therapy significantly reduced the incidence of local P. falciparum infection (Nosten et al., 2000). The widespread use of artemisinins and ACTs, along with ITNs or the IRS, also contributed to a significant decline in the overall incidence of falciparum malaria in Vietnam (Hung et al., 2002) and South Africa (Barnes et al., 2003) (Box 8-2) —both areas with relatively low EIR. It is still not known whether widespread use of ICT will lead to similar outcomes in areas of higher malaria transfer (EIR > 100). Unlike In Southeast Asia and South Africa, many malaria infections in sub-Saharan Africa, especially in older children and adults, are asymptomatic and untreated, but have a parasite density sufficient transmission (von Seidlein et al., 2002). In such circumstances, to reduce malaria transmission using gametocytocidal drug requires that asymptomatic as well as symptomatic carriers be treated. This led to the concept of mass drug use (MDA). During the MDA, the entire community of the population of the community, which contains many asymptomatic infected individuals receives treatment without first detection, which is actually parasites. MDA as a method to reduce malaria transmission gained momentum after 8-aminoquinolones (of which primine is the leading prototype) were discovered. This class of drugs is very effective in killing the gametocytes P. falciparum. One of the first studies to investigate 8-aminoquinolones as an MDA agent took place on a Liberian rubber plantation in 1930. Mass treatment with plasmoquine led to a significant reduction in the prevalence of parasites and a decrease in the number of infected mosquitoes in two treated camps (Barber et al., 1932). During the 1960s and 1970s, several other pages 214. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.1 ×7226/11017. This changed after improvements in vector control in KwaZulu Natal and neighboring southern Mozambique in 2000, and the implementation of artemisinin combination therapy (ACT), artemether-lumefantrine (AL), in January 2001. These interventions were followed by a 78 percent reduction in malaria notifications in the province within 1 year. In 2002, the number of notifications decreased by a further 75 per cent and this decrease was maintained in 2003 (Figs. 8.2-1). 8.2-1. Improved vector control and artemisinin combination therapy, artemether-lumefantrine, synergic effect on malaria transmission in KwaZulu Natal, South Africa. Reuse of DDT for indoor residue spraying of traditional structures (IRS) in March 2000. The introduction of the IRS in southern Mozambique in October 2000. In January 2001, the KZN for the treatment of uncomplicated falciparumalarium. SOURCE: Muheki C, Barnes K, McIntyre D. 2003. Economic assessment Recent malaria control intervention in KwaZulu, South Africa: SEACAT assessment. Sea cat. p. 215. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × The success of this double intervention further reflects an 89 percent reduction in both malaria-related hospital admissions (range 81-92 percent), and deaths (range 78-93 percent) across three rural district hospitals that serve the Ingwavuma community. Despite KwaZulu Natal also carrying South Africa's highest burden of the HIV/AIDS epidemic, the total number of all causes of hospital admissions was also reduced after improved malaria control. Dr. Hervey Vaughan Williams, medical director of Mosvold Hospital, a rural district hospital in Ingwavuma, reports that during the peak of the 2000 malaria epidemic, hospital admissions were averaging three patients per bed. Following a reduction in the overall number of hospitalisations, it is expected that the standard of care for all patients could be improved. These improvements in malaria control were also welcomed by local communities. During the focus group discussions on malaria there was a general enthusiasm for changes in the treatment of malaria. One woman in the household head reported: Every year I used to have malaria. This year I heard that new pills are coming. I was very sick with malaria. They gave me new pills ... (next) morning I did very well. ... I have been cultivated and harvested and I have never had malaria again this year. These remarks are in contrast to the views of female household heads on SP, such as those pills that were used before the current pills... most of us did not get down taking them ... because after using them you would feel as if malaria had become more severe than before. Public opinion that people with malaria urgently need to seek healthcare in the public sector are likely to have contributed to the pronounced public health impact observed after the AL implementation. These beliefs were described during focus group discussions: There is no way to treat malaria in addition to taking him to the clinic; When you waste time in sangoma [a traditional healer], you die. The long-standing benefits to public health following the introduction of artemether-lumefantrine in KwaZulu Natal are very encouraging. They reflect the benefits of the ACT by significantly reducing treatment failures and gametocytes transport speed, taking into account effective vector control, and relatively well-developed rural primary health care infrastructure. Karen Barnes, University of Cape Town (2003) Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. According to today's standards, studies were poorly designed and their results difficult to assess; however, in almost all cases, MDA was not able to stop transmission, although this significantly reduces the prevalence of parasites (Greenwood, 2004) (Box 8-1, The Garki Project). In 1981, the largest MDA programme produced essentially the same result. After one round of chloroquine and primaquine was given to about eight million people in Nicaragua, there was an immediate, marked decrease in clinical P. vivax malaria, but transmission continued and the incidence of malaria soon returned to its previous level (Garfield and Vermund, 1983). Most MDA tablets are administered, sometimes under supervision. Although it provides effective dosing, it is cumbersome. As an alternative to tablets, Pinotti developed the concept of drug delivery using medicated salt (Pinotti, 1954). In the 1950s, several studies of curative salts were carried out in endemic areas of malaria (Payne, 1988); these usually resulted in a reduced incidence of malaria clinical episodes associated with the cost of the rapid onset of antimalarial resistance (Meuwissen, 1964; Giglioli et al., 1967). It is now known that exposing malaria parasites to suboptimal doses of antimalarial drugs over time is the perfect way to insu provoke resistance. Thus, curative salt has no place in malaria control today. One MDA program included in another control intervention was recently reported from the island of Aneityum, Vanuatu. In this case, the effort was successful. Eight MDA rounds with chloroquine-SP-primahine combined with ITNs and environmental control measures prevented falciparum infection from the island (Kaneko et al., 2000). Antimalarial hemoprophylaxis is often used for short-term, nonimmune visitors in high-risk areas. Its direct benefits to individuals are obvious, but its indirect advantages include expanded international tourism, business travel and the economic development of the Malarios regions. However, the use of antimalarial drugs to protect the population of malaria endemic areas has always been more controversial (Greenwood, 2004). The following two sections collect past data and current trends in drug use to protect high-risk individuals in endemic areas of P. falciparum from acute infections. In 1956, McGregor and others reported the results of a study in the Gambia in which children received chloroquine every week from birth to page 217 share cite suggested citation:8 Malaria control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 × 2 those receiving chemotherapy patients had fewer episodes of malaria, increased better, and had higher mean hemoglobin values than children in the control group (McGregor et al., 1956). These findings were later reflected in studies in several other African countries (Prinsen Geerligs et al., 2003). A 1980 study using weekly maloprim (pyrimethamine plus dapsone) during the rainy season in children under 5 years of age was conducted in gambia (Greenwood et al., 1988). The overall mortality rate in children at the time of prevention was approximately 35 percent lower. Protected children also had fewer clinical attacks on malaria, and a higher average packed cell volume than control children. These results were maintained over a number of years (Allen et al., 1990) and are at least as impressive as the results obtained with ITNs. A recent study in Tanzanian infants taking Maloprim also showed a significant decrease in clinical attacks of malaria, and the incidence of severe anemia (Menendez et al., 1997). Antimalarial haemoprophylaxis in pregnant women was first studied at the Nigerian Mission Hospital in 1964 (Morley et al., 1964). Chemoprophylaxis with pyrimemamine significantly increased birth weight overall, but especially in infants born primigravidae (pregnant women for the first time). Subsequent studies in other African countries confirmed the positive effects of haemoprephylaxis on birth weight (Garner and Gulmezoglu, 2000) and maternal haemoglobin levels (Greenwood et al., 1989), especially during the first and second pregnancies (Greenwood, 2004). Medications used for hemoprophylaxis during pregnancy include chloroquine, pyrimamine, proguatil, maloprim, and meflitin. Although rarely implemented on any scale until recently, the WHO recommended that all pregnant women receive haemoprofofil with chloroquine in the second and third trimesters of moderate to high malaria transmission. Due to drug resistance, this policy no longer brings much benefit. Despite impressive results in clinical trials, targeted hemoprofile is never recommended for children living in malaria endemic countries, and it is rarely implemented in pregnant women. Concerns about cost, sustainability and security have contributed to its poor implementation (Greenwood, 2004). In addition, some experts are concerned that young children regularly taking hemoprephylaxis may notdevelop natural immunity. In gambia, children who received haemoprophylaxis for 4-5 years had experienced a statistically significant increase in clinical seizures page 218 Share Cite Recommended Quote: 8 Malaria Control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 × after the end of the prevention; however, the general protection from death extended to 10 years after the early years of antimalarial prevention (Greenwood et al., 1995). Final induction of drug resistance is possible in opposition to chemotherapy for chemotherapy in malaria-endemic regions. Although the unrestricted use of medicated salt and chloroquine and pyrimemamine in the 1960s contributed to the initial development and spread of drug resistance (Payne, 1988), there is little evidence to suggest that targeted hemoprofa reaction produces the same effect to any meaningful degree. Chemoprofphylaxis will inevitably lead to an increase in drug pressure, but it can be an acceptable price to pay if the benefits are large. The minimal risk of drug resistance could also be reduced through combination therapy in the future. Intermittent prophylactic treatment (IPT) is the full therapeutic course of antimalarial therapy at certain times, regardless of whether the recipient is infected. Unlike haemoprophylaxis (which aims to keep blood levels above the average inhibitory concentration for a longer period), IPT gives shorter breaks in the level of protective drugs, separated by periods when the level of the drug is too low to inhibit the growth of parasites. Overall, there are still many unknowns about the mechanisms of action of the IPT. For SP (the drug is most widely used in IPT in children and pregnant women), for example, it remains unclear whether IPT works primarily by eliminating existing parasites, or by the long-acting prophylactic effect of the drug (Greenwood, 2004). In Malawi, Schulz and others found that the full sp course, which is twice protected during pregnancy against low birth weight, is significantly more than weekly chloroquine hemoprofile (Schultz et al., 1994). In a Kenya-controlled study with IPTp with SP given two or three times during pregnancy, severe anaemia also decreased in women pregnant for the first or second time (Shulman et al., 1999). In another Kenyan area, however, HIV-infected women need more than two or three doses of IPTp to prevent placenta infection (Parise et al., 1998). Since all studies were conducted when P. falciparum was more sensitive than now, it is unlikely that IPT using SP would achieve the same effect today. WHO now recommends IPTp with SP to give each prenatal clinic a visit after resuscitation (usually between 16 and 18 weeks of gestation), replacing hemoprofifiaxis as the preferred method of Page 219 Share Cite Recommended citation:8 Malaria control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 × pregnancy (WHO/UNICEF, 2003). The benefits in HIV-infected women are unclear, however, as are the efficacy of IPTp in areas where malaria transmission is very seasonal or endemicity is low (SP resistance is particularly common in low transmission areas). Moreover, it is not yet clear what medicine or combination will eventually replace the intermittent pregnancy. The IPT concept was recently applied to prevent malaria in infants. In Tanzania, concomitant administration of a full dose of SP to infants with the second and third diphtheria-pertussis and maasle vaccines reduced the incidence of clinical malaria attacks and severe anaemia in the first year of life by 59 and 50 percent respectively (Schellenberg et al., 2001). Amodiaquine administered at the full therapeutic dose three times in the first year of life gave similar results (Massaga et al., 2003). Importantly, no rebound in malaria attacks or anemia occurred in the second year of life in children who received IPTi as infants. Studies of IPTi using SP are nearing completion in Ghana and Kenya, and further studies have recently started in Mozambique, Gabon, and Kenya. These trials will help determine under what conditions THE IPTi will prove to be the most effective, as well as the EIR threshold below which it will not be useful. In many areas of Africa, perhaps covering as much as 50 percent of the at-risk population, the main burden of malaria is not infants, but older children. This is particularly true in the Sahel and sub-Sahel countries, where malaria transmission is intense but seasonal. A pilot study in Senegal, which employs SP plus artesunate at 1-month intervals throughout the transmission season, is currently investigating whether the IPT principle can also be applied to older children (Greenwood, 2004). A correct and timely diagnosis of malaria is very important for an individual patient whose disease can quickly progress to a life-threatening stage. Rapid diagnosis, both on the individual and at the population level, is also an important tool for general malaria control. This section reviews currently available diagnostic methods, paying particular attention to the latest rapid tests that require relatively little technical knowledge. Such tests now facilitate the delivery of effective treatment in various 220-page numbers Share Cite Suggested quote:8 Malaria control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017. × low transmission settings, and eventually find your place in the malaria case, management of high transmission settings as well. Although studies have shown that healthcare providers cannot reliably identify malaria with clinical signs and symptoms alone (Weber et al., 1997; Perkins et al., 1997. Chandramohan et al., 2002), the use of clinical diagnosis is common in endemic areas. Ease, speed, and low cost are advantages of a presumptive diagnosis; deficiencies include overdiagnosis, which in turn contributes to wasted drugs, adverse drug exposure, and accelerating drug resistance, as well as insufficient malaria. As other common diseases, in particular acute lower respiratory tract infection in children, may mimic a clinical diagnosis may also lead to missed diagnoses of other curable diseases (Redd et al., 1992; Rey et al., 1996). In fact, the difficulty of distinguishing malaria from pneumonia was one of the main factors that led to the integrated management of childhood diseases (IMCI) -an algorithmic approach to treating sick children now used in many developing countries (Personal Communication, B. Greenwood, London School of Hygiene and Tropical Medicine, March 2004). Regardless of the theoretical pros and cons of a presumptive diagnosis, however, this is often all that is available. The current gold standard for daily laboratory diagnosis of malaria and surveillance cure is microscopic examination of thin and thick blood films stained by Giemsa's, Wright's, or Field Stain (Warhurst and Williams, 1996). In the thick technique of the film, a thick layer of blood containing several layers of red blood cells (RBC) is concentrated on a small area of the microscope slide. Red and white cell membranes are dispelled, and intracellular remnants are examined for the presence of plasmodial forms. Thin film technique is manufactured by single-order BC, facilitating species identification, and serial counting of parasites. Thin films are especially useful for severe malaria, both as a fast diagnostic test (White and Silamut, 1989), and a prognostic tool (Silamut and White, 1993; Phu and the Day, 1995). Although experienced microscopists can detect only 10-50 parasites/uL, and identify the species in 98 percent of visible parasites (Moody, 2002), topicality, obtaining such results requires a high level of skill and time, as well as optimal maintenance of equipment and reagents. Such conditions almost never exist in the periphery of health care in Africa, and other poor, malaria endemic locales around the world. p. 221. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. ×, one African study showed that the diagnosis of malaria with light microscopy reduces drug use (Jonkman et al., 1995). However, the current reality in many endemic circumstances is that clinicians question the reliability of light microscopy results or openly ignore them (Barat et al., 1999). Mixed infections (involving more than one plasmodial species) are also routinely under-reported with light microscopy (Personal Communication, N. White, Mahidol University, March 2004). The quantitative buffalo tongue test (QBC, Becton Dickinson) is a light microscopy modification that uses an affinity for the orange color of ordinary nucleic acid acridine, a fluorescent dye. This test was adapted to the malaria diagnosis using patented microhematocrit tubes, pre-coated with acridine orange and equipped with a plastic float that spreads buffy coat (white blood cells and parasite fraction of blood) toward the edge When centrifuged, malaria parasites and leukocytes take up paint and collect in a predictable place in the tube, where they can then be seen under ultraviolet light. In field studies, QBC was slightly more sensitive than normal light microscopy (Rickman et al., 1989; Tharavanij, 1990). Disadvantages of QBC are its need for electricity, special equipment, and supplies; its increased cost in relation to light microscopy; and was unable to distinguish P. falciparum from other human malaria species. The third diagnostic approach includes dipstick tests that eliminate the need for a microscope and detect parasite antigens in the blood using rapid immunochromatography using various antibodies. More than 20 such tests are currently being marketed and several are carried out in malaria endemic countries. Most are based on the histidine-rich protein 2 (HRP-2) found in P. falciparum. Compared to light microscopy and QBC, HRP-2 tests give a rapid and highly sensitive diagnosis of falciparum infection (WHO, 1996b; Craig and Sharp, 1997). The main drawbacks of HRP-2 tests are their high cost of the test (the lowest price of around 50 US cents) and the inability to quantify the infection's intensity. In addition, HRP-2 antigen may remain for several days or weeks after successful treatment. As a result, HRP-2 tests do not distinguish between hardened (i.e. drug-resistant) infections (WHO, 1996b). Several tests using HRP-2 to detect P. falciparum also include a second antigen to distinguish P. falciparum from other malaria species, although sensitivity is generally lower in P. vivax and others are not p. falciparum species (Murray et al., 2003). p. 222. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × OptiMAL is detected in OptiMAL sauce the parasitic enzyme lactate dehydrogenase (pLDH) actively produced by all malaria parasites during human erythrocyte growth (Piper et al., 1999). Unlike HRP-2, pLDH disappears from the bloodstream along with malaria parasites after successful treatment. OptiMAL also distinguishes P. falciparum from other malaria species without different levels of sensitivity to other malaria species. Overall, OptiMAL's field studies have been high, but the sensitivity in the last few studies has been unusual, possibly due to batch problems or poor testing (Murray et al., 2003). Quality control procedures for all types of rapid tests need to be improved. In selected tropical countries and in poor resource conditions where microscopy is not available or not reliable, RDT has great potential to reduce inappropriate antimalarial chemotherapy. On the one hand, it is much easier to train someone to perform RDT safely than to be a reliable microcopy. RdTs have been successfully used in remote tribal groups in forested areas of central India (Singh et 2000), refugee camps on the Thai-Burmese border (Bualombai et al., 2003) and rural health centres in Cambodia (Rimon et al., 2003). However, none of these areas affects the level of transmission of some very endemic areas in sub-Saharan Africa. The usefulness of antigen detection in areas of African hyperendemic malaria is not as clear as the tests are not quantitative, and only finding the parasite may be an insufficient basis for the diagnosis of malaria. One study in Zimbabwe indicated that mistreatment was reduced to 81 percent compared to a presumptive diagnosis (Mharakurwa et al., 1997). However, the improvement in diagnostic accuracy was most marked by the hypodenedemia in the region of the study. Overall, when the introduction of RDTs in areas of sub-Saharan Africa hyperendemic for falciparum malaria is still an open question. One of the perspectives on ttad use comes from Asia, where providing the means to diagnose and treat malaria at village level has coincided with a dramatic decline in morbidity and mortality. The fact that drug pressure is the main contributor to the transmission of resistant parasites is another reason why general treatment without RDT should not be allowed indefinitely anywhere in the world. However, in sub-Saharan Africa's high-prevalence areas, general treatment with clinically suspected clinically suspected cases of EDT is the safest short-term strategy, given the desperate need for rapid, in- or near-home treatment to save lives. After all, combining RDTs and ACTs in areas of Africa with low and moderate malaria prevalence could be Page 223 Share Cite Suggested quote: 8 malaria control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017. × reduce the number of diseases misdiagnosed as malaria and yield significant savings in drug costs and delayed onset of drug resistance. In the meantime, following the introduction of the AKT in Africa, pilot programmes and operational studies combining AKT and RDT should be promoted under different epidemiological conditions and risk populations. If malaria patients have parasites, their blood also contains malaria DNA and RNA. Applying a DNA probe to a filter paper with little space in human blood can identify malaria genetic material, including mutations or gene amplification conferring drug resistance (Plowe and Wellems, 1995). Today, such methods are increasingly being used to detect molecular drug resistances to chloroquine and SP markers. Until the filter paper has been properly treated, DNA can be recovered from them months after sampling (Farnert et al., 1999). DNA and RNA methods for the rapid diagnosis of malaria are currently impractical in most endemic regions, but their role may be extended in selected populations as tests become simpler and cheaper. Sensitive PCR methods can detect parasites density is as low as 1 microlithic, unlike 10-50 parasites per microliter with expert light microscopy (Greenwood, 2002). No malaria vaccine has yet been included in daily use, and safe and effective vaccines are at least another 10 years away (Greenwood and Alonso, 2002). This fact alone supports the central argument of this report, namely that the subsidy for effective treatment is an urgent priority, which cannot be expected until another control measure, such as a vaccine, is implemented. However, significant progress has been made in the research of malaria vaccines over the last two decades (Greenwood and Alonso, 2002). The most important labels are summarised below. The era of the malaria vaccine began in the 1970s when, based on previous work on rodent models, investigators from the University of Maryland demonstrated that irradiated P. falzoites and P. vivax were protected by naïve volunteers against infectious mosquitoes (Clyde, 1975). For the next 2 decades, the advance came mainly in experimental models rather than human trials (Kwiatkowski and Marsh, 1997). In 1990, the first report on the endemic field test of the vaccine field was published: a study on the preerythritis vaccine in Burkina Faso (Guiguemde et al., 1990). A recent meta-analysis of malaria vaccine studies documented 18 studies in 10,971 participants using pre-erythrocytic and blood-stage vaccines (Graves and Gelband, 2003). Tables 8-2 are listed as p. 224 in vaccine field trials. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 × TABLE 8-2 Of the candidate malaria vaccine clinical study group (field cooperation) Vaccine (type) Target Apovia, USA; New York University, USA ICC-1132 (protein) Pre-erythrocytic GlazoSmithKline Biologicals, Belgium; and WRAIR, USA (Medical Research Council [MRC] Laboratories, The Gambia; Centro de investigacao em Suade de Manhica [CISM], Mozambique) RTS,S (protein) Pre-erythrocytic Malaria Vaccine Development Unit, National Institutes of Health, USA Pvs25, AMA-1 (protein) Transmission blocking, blood stage Naval Medical Research Center (NMRC), USA; Vical USA Pf-CS, Pf-SSP2/TRAP, Pf-LSA-1, Pf-EXP-1, Pf-LSA-3 (DNA vaccines) Pre-erythrocytic New York University, USA CS (synthetic polymers, MAPs, polyoximes) Pre-EXP-1, Pf-LSA-3 (DNA vaccines) Pre-erythrocytic New York University, USA CS (synthetic polymers, MAPs, polyoximes) Pre--EXP-1, Pf-LSA -3 (DNA vaccines) Pre-erythrocytic New York University, USA CS (synthetic polymers, MAPs, polyoximes) Pre-EXP-1, Uk (MRC Laboratories, Gambia; Wellcome-Kenya Medical MVA Research Institute (KEMRI) cooperation, Kilifi, Kenya) DNA ME-TRAP, ME-TRAP, FP9 ME-TRAP, MVA-CS (DNA and recombinant virus) Pre-erythrocytic Statens Serum Institut (SSI), Copenhagen; Institut Pasteur; \windows\Lausanne Institute, Switzerland GLURP, MSP-3 (synthetic peptide) Pre-erythrocytes, blood walter and Eliza Hall Institute of Medical Research, Melbourne; Queensland Institute of Medical Research (QIMR), Brisbane; Swiss Tropical Institute; Biotech Australia Pty (Papua New Guinea Studies) MSP-1, MSP-2, RESA (protein) Blood stage Walter Reed Army Research Institute (WRAIR), USA (KEMRI, Kisumu, Kenya) FMP-1 (protein) Blood stage EXP = exported protein. LSA = liver stage antigen. MAP = multiple antigen peptide. Pvs = Plasmodium vivax surface protein. AMA-1 = aidic membrane antigen-1. RESA = ring-infected red cell surface antigen. SSP2 and TRAP are synonymous: sporozoite surface protein 2 and adhesion protein associated with thrombozoponidine. As of May 2003, only vaccines that are tested in clinical trials have been listed. Field collaboration is listed only if the candidate's field trials have started from May 2003. SOURCE: Moorthy et al. P. 225. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 × May 2003 (Moorthy et al., 2004). Additional individual antigens are currently present in various preclinical evaluations. A comprehensive discussion on all malaria vaccines is outside the scope of this report; however, some basic concepts and prototype vaccines are included below. For more detailed information on specific vaccine antigens and strategies, readers are focused on a number of excellent published reviews (Moore et al., 2002; Carvalho et al., 2002; Mahanty et al., 2003; Moorthy et al., 2004). In malaria endemic areas, natural human infection with P. falciparum induces a certain immunity that first protects against severe, then mild malaria (McGregor, 1974). Maintaining functional immunity requires repeated infectious mosquito bites, however (Cohen et al., 1961; Marsh and Howard, 1986). Of the 5,300 antigens encoded by P. falciparum, possibly 20 cause key protective immune responses to both major types of antibodies, and T-cell dependent, which follows natural effects (Moorthy et al., 2004). Unlike a natural infection, experimental vaccines traditionally targeted one of the three biological stages of malaria by its human or mosquito host: sporozoite, merozoite, or gametocyte. Pre-erythrocytic (or sporozoite) vaccines aim to block the initial penetration of sporozoites into human liver cells. The current candidate in this class is RTS, S– recombinant protein vaccine, which connects hepatitis B surface antigen DNA with DNA that encodes a large part of the P. falciparum circumsporozoite protein. In a randomised, controlled study in which three-dose RTS,S was expected in Gambian adults, vaccine efficacy was 34 percent during the 15-week follow-up period (decreased from 71 percent efficacy in the first 9 weeks to 0 percent over the next 6 weeks) (Church et al., 1997). Although short-lived, this vaccine-induced defense was the first defense against natural P. falciparum infection with pre-erythrocytic vaccines. Phase I studies rts, S in children aged 1-11 years in Gambia and Mozambique have now been completed, and the study in children 1-4 Mozambique currently has Way. However, it could be 10 years at least before rts, S finds a place in the daily immunization program, even if current pediatric trials are successful (Personal Communication, B. Greenwood, London School of Hygiene and Tropical Medicine, March 2004). Unlike the all-or-none protective action of pre-erythrocytes vaccines, merozoite (or blood stages) vaccines have two possible consequences: limiting RBC infestation, and reducing disease complications. Merozoite Surface Page 226 Share Cite Suggested Quote: 8 Malaria Control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. it forms the basis for a number of candidate vaccines. While some data suggest that vaccine-induced antibodies against MSP-1 may block natural malaria-protecting antibodies (Holder et al., 1999), an antiinsiable vaccine based on MSP-1 has now been moved to an adult Phase I study in western Kenya. Intravascular attachment of these zones to endothelial cells in the brain, kidneys and placenta is the most serious consequence of falcululrity. PfEMP-1 antigen is the main ligand for this sequestration event. Unfortunately, this high degree of variability of antigen, rapid rate of antigen variation and a large number of copies in certain parasites complicate the development of the vaccine. Some investigators still hope that the saved regions of PfEMP-1 can provide protective solutions for humans (Moorthy et al., 2004). Sexual-stage vaccines, rather than protecting vaccinated persons, are intended to reduce malaria transmission, especially in combination with other control methods. Their principle is as follows. Anti-gametocu antibodies induced vaccinated people enter female anophelines with blood products. These antibodies affect the development of parasites in the vector midgut, preventing further transmission. One of the main drawbacks of sexual stage vaccine candidates is the absence of commercial appeals by major pharmaceutical companies. Unlike, in particular, sporozoite vaccines (which could find an expandable market for tourists, migrants and military personnel entering malariotic areas) (Hoffman, 2003), it is unlikely that sexual-stage vaccines will be traded outside malaria endemic countries. A NIH-sponsored clinical trial of the P. falciparum gametocyte vaccine is currently being developed. The development of modern malaria vaccines has followed a somewhat opportunity course so far, guided by the findings of a specific antigen or enthusiasm of individual researchers (Greenwood and Alonso, 2002). However, as resources increase and more potential vaccine antigens are identified, it is essential to determine the primary characteristics of the malaria vaccine. An ideal malaria vaccine would inseems to lifelong sterilisation, ensure the protection of the usual EPI (extended programme immunisation) vaccines. Since none of these goals will be achieved quickly, vaccine researchers face a choice: either to work for a safe, highly effective and commercially viable vaccine (such as a pre-erythrocyte vaccine) for a short-term traveler or to work with a vaccine that offers long-lasting protection, aug-Page 227 Share Cite Suggested Cite Citation:8 Malaria Control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. For example, in semi-union recipients, a blood-stage vaccine that lowered the density of parasites may prove beneficial even if it had a minor effect on the incidence of infection. Similarly, a semi-effective preerythrocytic vaccine could protect against death from malaria, just as ITNs do. Whether or not an incomplete malaria vaccine justifies use in a particular environment will depend on its effectiveness compared to other available controls, its acceptability and its cost. Pregnant women in malaria endemic areas, especially primigravidae, have a particular need for improvedarial protection because malaria has a detrimental effect on pregnancy. In some areas, it becomes difficult to provide this protection by other means (e.g. haemoprofile or intermittent treatment). A vaccine that prevented sequestration of P. falciparum parasites in the placenta may reduce the chance of a pregnant woman giving birth to a low-birth weight baby, but will not protect her from anemia. For various reasons, including variations in malaria antigens and protein polymorphism, it is unlikely that any single malaria antigen will be found to meet all criteria for a perfect vaccine. Thus, the most effective malaria vaccine could contain a cocktail of antigens from the same stage of the parasite's life cycle, or different antigens from different stages. The most widely tested combined vaccine to date is SPf 66, which includes several erythrocyte-stage antigens that were originally found protective in Colombia (Pattarroyo and Armador, 1999). However, studies using SPf66 in African holoendemic areas found marginal protection, if any (Alonso et al., 1994; D'Alessandro et al., 1995), nor does the vaccine grant protection to Infants of Tanzania when administered as part of the original EPI vaccine package (Acosta et al., 1999). The vaccine also failed to protect Karen children in the malarios region of northwest Thailand (Nosten et al., 1996). The first multi-stage, multiantigen P. falciparum vaccine candidate was NYVAC-Pf7, a revived vaccinia virus that has been genetically engineered to include seven P. falciparum genes encoded before erythrocyte antigens CSP and LSA1; aborn blood-stage antigens MSP1, AMA1 and SERA; And PFs25 (Tine et al., 1996). Initial studies did not show protection against P. falciparum in human volunteers, although detectable immune responses were observed (Ockenhouse et al., 1998). MuStDO (Multi-Stage Malaria DNA Vaccine Operation) is a permanent collaboration involving several scientific institutions around the world, including the Marine Medical Research Center (NMRC), the U.S. agency page 228 Share Cite Recommended Quote: 8 Malaria Control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × International Development (USAID), Noguchi Memorial Institute of Medical Research in Akra, Ghana and Navrongo Health Research Center in Navrongo, Ghana. The experimental mustdo vaccine development is currently focused on 15 P. falciparum antigens (5 pre-erythrocytic and 10 erythrocytic proteins) (Kumar et al., 2002), although future versions may also include transmission-blocking antigens. Choosing which malaria antigens to be administered in clinical trials was not a major problem if there were relatively few candidates to choose from. However, characterizing P. falciparum genomes has now identified hundreds of parasite proteins that could potentially be tested as separate components of the vaccine. In selecting the following components of the vaccine, the following vaccine components should be applied: (1) evidence that the antigen plays an important role in the survival or pathogenicity of the parasite; 2) evidence from animal experiments that the antigen in vivo insuses protective immunity; and (3) evidence that the immune response to antigen is related to protection (Greenwood and Alonso, 2002). If a vaccine candidate undergoes phase I and PHASE II testing, additional considerations for the development of phase III studies include study site, study population, study size and appropriate clinical endpoints (Table 8-3). Another important factor influencing the introduction of a semi-effective malaria vaccine in everyday use will be its cost-effectiveness compared to other malaria control measures such as ITN (Graves, 1998; Goodman et al., 1999). TABLE 8-3 Possible endpoints in Phase III malaria vaccine trials End Point Advantages Disadvantages Death The most important public health end point Requires a large study of malaria mortality rate Hard to measure severe clinical malaria Important end point Requires high hospital admission rates Mild, clinical malaria Requires relatively small study May miss the effects of severe disease Parasitemia Easily measured Can miss important clinical effects SOURCE: Greenwood and Alonso (2002). p. 229. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × Regardless of when and where vaccination is widely used, it is unlikely to replace the need for effective treatment of drug-resistant falciparum malaria for several decades (Personal communication, B. Greenwood, London School of Hygiene and Tropical Medicine, March 2004). In recent years, there have been several historical examples of malaria control in endemic areas by combining

environmental and human intervention. In the south of 1930 and 1940, Brazil, Egypt and Zambia operated successful multilateral approaches to control the leadership of A. gambiae (Utzinger et al., 2001; Killeen et al., 2002). In Zambia's copper mines, clearing vegetation, converting river boundaries, draining swamps, and applying oil to open bodies of water along with house screening, mosquito nets, and quinine treatment reduced the local morbidity of malaria by 70 to 95 percent over 30 years (Utzinger et al., 2001). Today, modern versions of such programs are run by Exxon-Mobil in Cameroon and Chad, British Petroleum in Angola, and the Konkola copper mine in Zambia. In addition to commercial activities with a financial incentive to protect workers or citizens from malaria through various combinations of environmental and vector control measures, as well as chemotherapy, local health authorities are sometimes mounted integrated malaria programmes in a conventional health structure that includes some or all of these elements (Shiff, 2002). Needless to say, such programmes require coordination and planning, cooperation with local communities, and sustainable funding. The campaign, which brought together the local epidemic of the IRS and the combination of artemisinin in KwaZulu, South Africa (in response to the multidrug resistant Plasmodium falciparum), is the latest example of a successful government-sponsored integrated control programme (Muheki et al, 2003). In recent years, studies in Sierra Leone (Marbiah et al., 1998) and Gambia (Alonso et al., 1993) have also supported ITN packaging, as well as targeted haemoprophylaxis as a successful control package. On the other hand, the systematic deployment of AKT in refugee camps on the north-western border of Thailand (120 000 inhabitants) resulted in a sustained reduction of more than 90 per cent in the number of cases of falciparum malaria without additional control intervention (Nosten et al., 2000). Page 230 Share cite suggested quote:8 Malaria Control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. Although urban centres traditionally experience lower rates of malaria transmission than in rural areas, the rapid growth of the world's urban population has a significant impact on the epidemiology of malaria (Robert et al., 2003). This is particularly the case in sub-Saharan Africa, continent (United Nations, 1999). In 1900, 10 percent of Africans lived in urban areas, but today nearly half the population of sub-Saharan Africa lives in urban or suburban areas. This proportion is expected to continue to increase over the next 25 years. In fact, many African cities have unique features that still prefer the transmission of malaria. Unlike Western cities with their different land use patterns, housing construction, utilities and social services, many African cities do not have such infrastructure and include larval habitats such as rice fields and garden wells adjacent to residential, market and commercial areas (Robert et al., 2003), as well as suburban slums and shantytowns. Limited data also suggest that some anophelin vectors can adapt to urban ecology. In Akra, Ghana, Gambia has adapted to water-filled inland containers and contaminated aquatic habitats (Chinery, 1990). In a recently urbanized area of Kenya, A. gambiae also raised in temporary man-made places during the rainy season (Khaemba et al., 1994). With the exception of large private activities, it is currently considered that the long-term reduction of malaria through vector control alone is almost impossible in high and medium transmission areas (Trape et al., 2002). On the other hand, areas with naturally low or unstable transmissions, such as highlands, mountain areas, semi-dry regions and urbanised areas, are much more subject to vector control. As urbanization progresses, anofelin-growing sites in African cities should decline and localize, thus facilitating control by classical methods such as drainage, larviciding, and indoor spraying (Trape and Zoulani, 1987; Trape et al., 1992). In the future, the upside of sub-Saharan urbanisation may be the creation of malaria-free zones, which create a significant proportion of the country's population. This success could, in turn, stimulate the expansion of eradication efforts through vector control and other integrated interventions. Malaria epidemics usually occur in regions where transmission is low or not most of the time and populations lack protection immunity, although epidemics can also strike higher transmission areas where there is a breakdown in health or environmental services, increased drug resistance, or recent immigration of non-inmunirant individuals (for example, laborers come to Page 231 Share Cite's suggested quote: 8 Malaria control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 × during construction or other development project). Climate change also contributes to the development of epidemics. In terms of population impact, two common features of almost all malaria epidemics are: (1) the same risk of clinical illness and death among children and adults and (2) clinical outweighs and overcomes available health services (Snow and Gilles, 2002). From that, in endemic areas, the climate often restricts the transmission of malaria, i.e. normal conditions are either too dry, too wet or too cold for the distribution of vectors or parasites. In such places, minor environmental changes can lead to an epidemic. The el Niño Southern oscillations (a weather event originating in the Pacific Ocean but having wide global consequences, in particular drought and floods) have been particularly well researched in this respect (Kovats et al., 2003). For example, El Niño-related droughts are linked to malaria outbreaks in Sri Lanka (Bouma and van der Kaay, 1996), Colombia (Poveda et al., 2001) and Irian Jaya (Bangs and Subianto, 1999). In the highland regions, the elevated temperatures in El Niño may increase the transmission of malaria, as happened in Northern Spain in 1981-1991 (Bouma et al., 1996). Higher than normal temperatures and heavy rainfall have also contributed to short-term increases in the highlands of malaria in Rwanda (Loevinsohn, 1994) and Uganda (Lindblade et al., 1999). Despite the impact of climate change on malaria in the highlands, new evidence suggests that drug resistance has affected upland epidemics in East Africa to a much greater extent than any other environmental factor (Hay et al., 2002). For example, chloroquine resistance has been identified as a key factor in the regeneration of malaria in Kericho Tea Manor in Kenya, where the climate, environment, human population, health care provision, and malaria control measures remained stable (Shanks et al., 2000). Similarly, the regeneration of malaria in the Usambara mountains of Tanzania is now associated with an increase in antimalarial drug resistance (Bodker et al., 2000) as opposed to previously postulated climate change (Matola et al., 1987). There are many causes for mass migration: war and civil strife, economic resettlement, environmental and natural disasters. Under appropriate circumstances, this mobility may affect the transmission of malaria. Among the 20 countries at high risk of malaria transmission in America, 16 identified human mobility as the main cause of persistence in transmission (PAHO, 1995). Migration is also linked to the spread of drugs- Page 232 Share Cite Suggested quote: 8 Malaria control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. Thimasarn et al., 1995; Kazmi and Pandit, 2001). In Kenya, the seasonal movement of many low-income workers to upland tea plantations has led to epidemics (Malakooti et al., 1998; Shanks et al., 2000). The seasonal influx of central and South American migrant farm workers has led to local malaria outbreaks in the United States (Zucker, 1996). Similar data link malaria outbreaks with political upheaval Migration. In South-East Asia, malaria was the main cause of morbidity and mortality among Cambodian refugees after arriving in eastern Thailand (Glass et al., 1980) and Karen refugees in western Thailand (Luxemburger et al., 1996). In Central Asia, the civil war and the collapse of health care infrastructure led to the re-formation of malaria in Tajikistan (Pitt et al., 1998). In East Timor and Afghanistan, recent aid efforts were complicated by malaria (Ezard, 2001; Sharp et al., 2002b). African examples are the most. To name a few: malaria was the leading cause of death among Mozambique shelters in Malawi and Ethiopian refugees in Eastern Sudan, while malaria fever was second only to laxative disease as the main cause of morbidity and mortality among Rwandan refugees entering the eastern zakar (now the Democratic Republic of Congo) (Bloland and Williams, 2002). After mass migration in the malariozem region, additional risk factors for malaria outbreaks are as follows: non-standard housing and environmental protection from night anophelin bites, deliberate redeption, overcrowding, proximity to livestock, low socio-economic status, poor nutritional status, lack of immunity from malaria, destruction or excessive burden of existing infrastructure, and injustice to volatile health services (Bloland and Williams, 2002). One of Roll Back Malaria's efforts to reduce the African malaria burden is to apply malaria early warning systems (MEWS) to respond quickly to the epidemic (WHO, 2000; WHO, 2001). Specifically, Abuja aims to identify and respond to 60 percent of the malaria epidemic in Africa within 2 weeks of occurrence and detection (WHO, 2001). The main tools for MEWS are: Prediction (usually related to seasonal climate predictions) Early warning (monitoring meteorological conditions such as rainfall and temperature) Early detection (based on daily clinical monitoring) Page 233 Share Cite Suggested quote: 8 Malaria control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × Although RBM reports that MEWS is generally performing well in South Africa and programs have begun in Ethiopia, Kenya, Uganda, Tanzania and Sudan (WHO/UNICEF, 2003), the recent discovery of epidemics in Kenya reveals. In the summer of 2002, early warning, based on district-level rainfall estimates, had the potential to detect two epidemics in four upland areas of southwestern Kenya. Warnings in a particular area could be warned of possible exceptional circumstances for 4 weeks. In this case, not only did the early warning system not work, early detection based on outpatient monitoring was also delayed, as reporting was only carried out on a monthly basis. Authors' retrospective analysis of 2002 Kenya experience supports better planning based on known seasonal epidemiological risks et al., 2003). In order to respond in a timely and effective manner to a possible malaria epidemic, it is usually necessary to deploy additional drug supplies, to use highly effective treatment and, in particular, to control vectors, in particular the widespread IRS (Luxemburger et al., 1998; Rowland and Nosten, 2001). Rapid diagnosis is also important during the rapid influx of refugees; in such situations have proved to be very useful (Nosten et al., 1998). In addition, a drug treatment policy is needed that takes into account the immune system condition of the victims. Artemisinin-based combinations are particularly attractive during epidemics because they are clinically useful and independently affect the transport of gametocytes (which, in turn, reduces transmission). Since epidemics are often associated with a large proportion of the population in a relatively short period of time, one or more rounds of mass drug use, together with other control measures, are another possibility to quickly put an end to the outbreak (von Seidlein and Greenwood, 2003). If the MDA is selected, the drug selected is necessary to kill gametocytes. It should also be provided as soon as possible, which poses a major logistical problem. Malaria control cannot be a campaign; it should be a policy, a long-term programme. This cannot be done with an spasm of effort. It requires the adoption of a practical program ... which will be maintained for a long time. (Boyd, 1949) p. 234. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × The malaria control strategy approved by the WHO in 1979 highlighted the need for flexibility in the programme, namely the adaptation of all and all available methods to realistic objectives set by national health authorities and possible within the limits of human and material resources (WHO, 1979). Then, in October 1992, in October 1992, at the WHO Ministerial Conference on Malaria (WHO), Article VIII of the World Declaration on Malaria Control (WHO) issued this landmark: We commit to controlling malaria and will plan malaria control as an essential component of national development. In fact, however, the last decades of the twentieth century experienced a steady decline in malaria control as countries moved from large vertical drive organizations focused on the IRS and malaria eradication (of course, many such programs were flawed) to a new common denominator: a village health worker with a jar of chloroquine tablets (Personal Communication, B. Greenwood, London School of Hygiene and Tropical Medicine, March 2004). Some countries like India kept their central control programs after the eradication era ended, but most African countries did not. Today, many African countries are painstakingly renewing their national programs to access new resources for malaria control available through the Global Fund other donor agencies. Although the purpose of this report is not to recommend an ideal template for controlling national malaria, some general observations are in order. Today's malaria control programme must have at least five components: a public health surveillance system, medical services, preventive measures, a community engagement programme and the ability to carry out specific studies (operational studies) as appropriate (Bloland and Williams, 2002). Specific functions that should also be performed at national level include monitoring drug resistance and pharmacovigilance to investigate adverse or unexpected effects of new antimalarial therapies such as the AKT. Instead of returning to a massive yet narrowly focused organization in the past, resurrected programs should take a middle ground between a centrally driven structure and one that allows full participation at all levels of the health care system. In addition, public malaria programmes should consider creative partnerships with the private sector. Some examples of contemporary public-private synergy could be training private practitioners in the treatment of malaria; state-sponsored social marketing campaigns to complement the sale (or subsidised distribution) of itn; or state licensing of pharmacies with staff certified to dispense antimalarials, and other essential drugs in the periphery of health care. p. 235. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017. × Today, rapid and effective treatment is key to reducing drug-resistant malaria's increasing morbidity and mortality. Therefore, a rational antimalarial drug policy is an essential element of any national malaria control programme. As many countries with increasing resistance to first, second and even third-row antimalarial medicines are burdened with debts and poorly funded health budgets, the changes to antimalarial drug policy are economically daunting. The policy change process can also be time-consuming and involved. A detailed analysis of Kenya's changes from chloroquine to SP highlights the complexity of the decision-making and implementation process, even if the two drugs have similar costs (Shretta et al., 2000). Chloroquine resistance was first recognized at a meeting organized by the Kenya Institute for Medical Research in January 1989. In 1991, the Ministry of Health requested a review of the scientific evidence in support of the review. In October 1997, a draft guideline was finally released, reflecting more than 20 independent studies over a 14-year period documenting the failure of chloroquine. Even after consensus has been reached, several factors may delay national implementation for another 18 months or more: political and financial support, training for healthcare providers and general sensitisation it is essential that the antimalarial transition is successful (WHO/UNICEF, 2003). In the future, a culture will be crucial in which changes in the treatment of malaria can take place on a fairly regular basis, based on sound evidence. This is happening to some extent now (e.g. in Kenya and Tanzania), but much more flexibility, and a rapid response is needed in most malaria endemic countries. In 1993, Malawi was the first sub-Saharan country to transfer from chloroquine to SP as first-line treatment for p. falciparum. Between 1998 and 2001, Kenya, Uganda, Tanzania, Zanzibar, Rwanda and Burundi followed suit (e.g. Malawi, they either opted for SP monotherapy, or SP plus a combination of chloroquine or amodiaquin). The countries that have now adopted and (most recently) implemented the AKT are Tanzania (Zanzibar) (2001), Zambia (2001) and Burundi (2002). In South Africa, the provinces in which the ACT is fully implemented are KwaZulu Natal (Coartem) and Mpumalanga (artesunate+SP) (WHO/UNICEF, 2003). The first-line antimalarial drug policy for certain African, Asian and South American countries is listed in Tables 8-4 as from March 2003. p. 236. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017. × 8-4. TABULA Valstis/reģioni, izmantojot ACT kā pirmās rindas terapiju nekomplicētu malārijas reģiona/valsts pirmās rindas ārstēšanai Āfrikas reģionā Burundi AS+AQ Komoru salas AL Dienvidāfrika (KwaZulu Natal) AL Zambija AL Zanzibar AS +AQ Western Pacific Region Cambodia AS(3d)+MQ China, Yunnan, Hainan ATM/AS(5d) Lao PDR AS+MFQ Vjetnama, north ATS/AS(5d)+PQ Viet Nam other AS(3d)+MQ25 South-East Asia Region Bhutan MQ+AS(3d) Myanmar AS(3d)+MQ Thailand MQ+AS(3d) Region America Bolivia MQ15+AS(3 d)CQ+PQ Gviāna AL Peru (Amazones apgabals) AS(3d)+MQ AS(3d)+SP Surinama AL=Artemether-lumefantrine AQ=Amodiaquine AS=Artesunate ATM=Artemether ATS=Artemisinin CQ=1 Hlorokvīns MQ=meflikinātīns MQ15=meffokvīns 15 mg/kg MQ25=meflokvīns 25 mg/kg PQ=primārais līmenis Q=hinīns SP=sulfadoksīns-pirimetamīns T=tetraciklīns AVOTS (no marta , 2003): Page 237 Share Cite Suggested Quote: 8 Malaria Control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017. × currently, most control policies are still organised at national or local level (Kaul and Faust, 2001), but interest in the regional approach is growing. On the one hand, individual countries can no longer take decisions on drug policy in isolation. Given the flowing nature of borders, they now understand that their and their neighbours' policies affect each other. More and more are being called upon to with the information between the countries on their respective malaria situations, malaria treatment policies and approaches used to combat drug-resistant malaria. Acknowledging that a regional approach offers a better platform for addressing the problems of controlling malaria affecting policy, a number of networks and initiatives have been set up, in particular, the East African Antimalarial Treatment Monitoring Network (EANMAT), West African Antimalarial Monitoring Networks (WANMAT I and II), South Africa's Combined Antimalarial Therapy (SEACAT), the Central African Network (Réseau d'Afrique Centrale des Thérapeutiques Antipaludiques or RACTAP), the Amazon Malaria Initiative (AMI) and the Asian Cooperation Training Network for Malaria (ACTMalaria). These networks focus on partnership and common objectives in the control of malaria, with a particular focus on training, research and operational issues. In anticipation of full implementation in Africa and elsewhere, one of the current dilemmas that many malaria endemic countries face is the practical question of when, in the face of increasing resistance to antimalarial drugs, changes in drug policy should be implemented. Should it start early when only a small part of the population is at risk, or at a later stage when the risk affects a larger proportion of the susceptible population? Until recently, the WHO recommended changing more effective treatment if clinical failure rates exceeded 25 percent in 14 days after treatment; it has now lowered the ceiling to >15 per cent clinical and >25 per cent total failure (i.e. clinical + parasitologic [WHO/HTM/RBM/2003.50]). No matter what standard threshold is chosen, the single points of change do not take into account areas where malaria is seasonal or epidemic, and therefore local population groups are more vulnerable to adverse clinical outcomes from drug-resistant malaria. In addition, many authors have noted that the initial WHO response categories (benevolence, warning, action and change) were developed in response to the relatively slow rate at which chloroquine resistance occurs. Unlike chloroquinone and amodiaquin SP, resistance is rapidly occurring and spreading in high-transmission areas (Talisuna et al., 2002). Finally, there are technical questions about the WHO test itself. Since it does not provide information on treatment failure after 14 days, many Page 238 Share Cite Suggested quote: 8 Malaria Control. Institute of Medicine. 2004. Saving Lives, Buying Time: The Economy of Malaria drug in the era of resistance. Washington, DC: National Academy press. doi: 10.17226/11017 doi: 10.17226/11017 ×. A recent analysis of a sample consisting of 23 percent of all randomized studies published since 1965 suggests that the 14-day test could miss as many as 63 to 100 (Stepniewska et al., press). In general, from 2004, malaria control can be considered either a cup half full or half empty. On the positive side: more money has become available for malaria control (though not nearly enough), prolonged ITNs are finally becoming a reality, combination therapy with artemisinins is more widely available than in the past (although a radical solution is still needed for ACTs to reach most malaria sufferers, especially in sub-Saharan Africa), and vaccine research. Vector control and ITNs will never have a major impact in many areas of Asia, on the other hand because of local vector behavior; the main strategy there must be effective treatment. And despite many serious hopes for a vaccine solution to the global malaria problem, vaccines are far from ready and will never control malaria by themselves, Africa in particular will always play a role in vector control and drugs. Improved drug delivery (including the management of severe malaria at home with APT) is another practical issue that is currently under consideration, but will require even more attention after effective first-line treatment reaches Africa.

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